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Editor

PAUL W. CLOUGH
Assistant Editor

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ANNALS OF INTERNAL MEDICINE

VOLUME 43 JULY, 1955 NUMBER 1

PREVALENCE AND NATURE OF HEPATIC DISTURBANCE FOLLOWING ACUTE VIRAL HEPATITIS WITH JAUNDICE*

By JOHN R. NEEFE, M.D., F.A.C.P.,† JOSEPH M. GAMBESCIA, M.D., *Philadelphia, Pennsylvania,* CHARLES H. KURTZ, M.D., *Lancaster, Pennsylvania,* HUGO DUNLAP SMITH, M.D., *Cincinnati, Ohio,* GILBERT W. BEEBE, Ph.D., SEYMOUR JABLON, M.A., *Washington, D. C.,* JOHN G. REINHOLD, Ph.D., *Philadelphia, Pennsylvania,* and S. CLAY WILLIAMS, M.D., *Winston-Salem, North Carolina*

THE apparent initiation of chronic liver disease by acute illnesses presumed to be acute viral hepatitis now has been observed sufficiently often to warrant serious consideration of this infection as a potential cause of chronic liver disease.[1-8b] However, the exact nature of this relationship, the frequency with which chronic hepatic disease is initiated by acute viral hepatitis, and the factors responsible for this presumed sequence of events have not been well defined. Because of the high incidence of acute viral hepatitis in the military services during recent years and of the availability of facilities organized by the National Research Council (NRC) for medical follow-up studies on veterans, the NRC Subcommittee on Liver Diseases

* Presented at the Thirty-sixth Annual Session of the American College of Physicians, Philadelphia, Pennsylvania, April 26, 1955.

From the Gastro-Intestinal Section of the Medical Clinic, the Department of Medicine, the Department of Pediatrics, and the William Pepper Laboratory of Clinical Medicine, Hospital and Medical School of the University of Pennsylvania; and from the Division of Medical Sciences, National Research Council.

This investigation was carried out under contracts between the Veterans Administration and the University of Pennsylvania, and the Veterans Administration and the National Research Council. This is a report from one of the three centers (Minneapolis, New Orleans and Philadelphia) collaborating in a study supported by the Veterans Administration under the program of medical follow-up studies organized by the NRC Committee on Veterans Medical Problems.

† Represents work done as a National Research Council Senior Fellow in the Medical Sciences (1946-49).

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recommended in 1947 a clinical follow-up study of veterans as part of the NRC program and outlined specific plans for its conduct at three university centers.

In accordance with the broad plan of study recommended by the Subcommittee on Liver Diseases of the NRC, hepatitis follow-up centers were organized at Tulane University School of Medicine (Roy H. Turner, M.D., Director), at the Minneapolis Veterans Administration Hospital under the University of Minnesota Medical School (Leslie Zieve, M.D., Director), and at the School of Medicine of the University of Pennsylvania (John R. Neefe, M.D., Director). At each of these centers plans were made to survey, in as uniform a manner as possible, persons falling into the three following categories:

1. *"Posthepatitis" Group:* Representative veterans known to have had an illness during World War II that warranted a diagnosis of acute viral hepatitis with jaundice.

2. *"Heavy Exposure" Group:* Representative veterans known to have had an extraordinary opportunity for exposure to hepatitis virus during World War II but who apparently did not develop clinically recognizable hepatitis with jaundice.

3. *"Minimal Exposure" Group:* Representative veterans who had not had any recognized unusual exposure to hepatitis virus. The term "minimal exposure" has been used in preference to "control" because of the apparent high incidence of unrecognized infection with hepatitis virus and the inability to determine accurately the occurrence in the past of such infection, especially of the non-icteric type.

Our study (University of Pennsylvania) differed from those at the two other centers only in that the following additional groups were available to us for follow-up study: (1) a group of civilians, each of whom was known to have been infected with the IH (A) type of hepatitis virus ("Posthepatitis" Camp Group) or heavily exposed to it ("Heavy-Exposure" Camp Group), who will be referred to as the "campers"; (2) a group of medical students, some of whom served as controls for the establishment of "normal" values for tests employed, which subsequently was included in the "minimal exposure" group. The individuals in this group who were utilized as "controls" will be referred to by that designation.

The present report, representing studies carried out between 1946 and 1950, includes only the data obtained at the Philadelphia (University of Pennsylvania) follow-up center. The report from the Minneapolis (University of Minnesota) center has been published elsewhere,[9] and the data of the Tulane center will be published later.

Sampling Considerations

In accordance with a uniform sampling plan devised for all three university centers, the Philadelphia center was allocated samples of veterans as follows:

Posthepatitis Group: The Surgeon General, U. S. Army, provided machine-listings covering 1942–1945 Army admissions for hepatitis and, for 1942 cases, certain related diagnoses, on the part of enlisted men whose Army serial numbers (ASN) were indicative of induction in the Third Service Command. The listing of 7,706 admissions was first reduced to 1,643 on the basis of ASN blocks for the Philadelphia area; the number was then reduced, at random, to 596 cases. Efforts to locate the 596 cases during the survey period, 1948–1950, revealed only 134 resident in the city of Philadelphia at the time they were called, of whom nine were rejected as having inadequate evidence of a history of acute viral hepatitis. A definite history of jaundice, otherwise unexplained, was required for acceptance in this group.

Heavy Exposure Group: The major World War II epidemics of infectious (virus IH or A) hepatitis were in the Fifth Army in Italy in the fall of 1943 and 1944, and in the Sixth Army on Luzon in 1945. The corresponding division-months were arrayed and heavy exposure was defined arbitrarily as presence in a division for a month immediately preceding one in which incidence for that division reached 263 or more admissions per 1,000 strength per year. A search was made of payroll rosters for infantry regiments, field artillery battalions, and engineer units in the 15 division-months thus isolated, and men were chosen initially on the basis of ASN blocks *without regard for their medical history.* Men living in metropolitan Philadelphia were allocated to the center, which assumed the responsibility for separating them into posthepatitis cases and others. The latter were then designated as the "heavy exposure group" on the assumption that, if subclinical or inapparent infections do occur, such a group had a high chance of including them. That this group was exposed to infection is supported by the fact that, among 465 cases so allocated to all three centers for classification into two groups and follow-up, 98 (21%) were found to have had acute viral hepatitis with jaundice. The initial Philadelphia allocation was 143 such cases. Excluded from the allocation for clinical study were all deaths prior to that point, and two men who at follow-up were back in service, but who had recovered from their hepatitis and had been demobilized on points in 1945.

Minimal Exposure Group: Controls resident in metropolitan Philadelphia were chosen at random within appropriate ASN blocks, except that the following circumstances were disqualifying: entry into service before January 1, 1943, or after August 1, 1945; vaccination against yellow fever; any serious injury which might have required administration of blood or plasma; any transfusion of blood or plasma; diagnosis of syphilis, gonorrhea, malaria, atypical lichen planus, or liver disease; history of jaundice prior to induction, and service in an epidemic area. The Philadelphia center received an allocation of 168 such controls.

Camper Groups: In 1944 an extensive water-borne epidemic of (virus IH or A) hepatitis occurred in a civilian summer camp near Philadelphia and

extensive etiologic and epidemiologic studies were carried out by Neefe and Stokes.[10] All persons at this camp were heavily exposed but not all acquired apparent infections. *Two camper groups* were established, a posthepatitis (146 campers) and a heavily exposed (46 campers) group; both sexes and a wide age range are represented in these two camper groups.

Control Group: Members of the first- and second-year classes in the School of Medicine of the University of Pennsylvania in 1947 were utilized as a *supplementary control group,* provided their medical histories suggested no illnesses, exposure, habits, etc., likely to lead to liver injury. None had had military service beyond that associated with academic training programs in the United States. In all, 142 men were chosen for study and were examined.

Military records on the three *veteran* groups were abstracted by National Research Council personnel according to a scheme which provided the

TABLE 1

Number of Individuals Examined at Philadelphia Center, by Survey Diagnosis and Source

Survey Diagnosis	Source			
	NRC Allocations of Veterans	Medical Students	Campers	Total
Posthepatitis				
IH or SH	44		0	44
IH	53		145*	198*
SH	29		0	29
Total	(126)		(145*)	(271*)
Heavily exposed	92		46†	138†
Minimally exposed	100	142	0	242
Total	318	142	191	651

* Includes 70 females.
† Includes 15 females.

details of diagnosis and disposition for every illness involving loss of time, and for all out-patient visits except those for surgical and dental conditions. Veterans were located through the facilities of the Veterans Administration, and letters were sent by the senior author outlining the objectives of the study and emphasizing the advantages of the examination to the individual. If repeated letters and telephone calls were of no avail, a social worker made a home visit to encourage participation in the study. By these methods it was possible to bring under observation, from among the three veteran groups as allocated, 82% of the posthepatitis cases, 79% of the heavily exposed, and 62% of the minimally exposed. Although the campers were more widely dispersed geographically than the NRC allocation, it was possible to bring under observation 57% of the posthepatitis camper group.

To enable an indirect exploration to be made of the extent of any bias

arising from incomplete follow-up in the veteran and camper groups, those who responded promptly were compared with those who required a great deal of persuasion. These comparisons disclosed no evidence of bias in the veteran posthepatitis cases, but campers who reported on the basis of a single letter reported many more symptoms than those who came less readily; however, these two groups of campers did not differ as to objective findings.

On the basis of abstracts of previous medical records and detailed histories obtained at the follow-up examination, all cases were given a final "survey diagnosis," the classification for which appears in table 1. A definite history of jaundice was required for assignment to the posthepatitis group. Viral hepatitis is known to be caused by at least two immunologically distinct types of hepatitis virus.[7, 11, 12] Each type may or may not include one or more similar strains, and other as yet unrecognized types or strains may exist. That virus which is responsible for the naturally occurring epidemic disease, usually acquired by the intestinal-oral route, and with the "short" incubation period of two to six weeks, has been referred to as infectious or virus IH hepatitis. (The designation virus A has also been suggested.) The virus responsible for the "long" incubation (one and one-half to six months) form of so-called homologous serum hepatitis will be referred to here as virus SH (also called by some virus B) hepatitis. When available epidemiologic data were sufficient to justify classification of the reference illness of posthepatitis veterans as either IH or SH type, this distinction was made to permit study of any differences in residual effects from the two types of infection. Frequently, as usually was the case with isolated infections, epidemiologic data were not conclusive and did not warrant specific classification of the reference illness as IH or SH type infections. Under these circumstances, the illnesses were classified as "either IH or SH." This group thus probably includes both types of infection.

The Follow-up Examination

If the *reference point* be defined as the date of onset of hepatitis for "posthepatitis" cases, the date of first heavy exposure for the "heavy exposure" group, and the date of entry into service for the "minimal exposure" group and the "local controls" with military service, then the follow-up examination was done approximately six years after the reference point for virus SH cases, four and one-half years for all other veterans in the NRC allocation, and four years for the campers. Veterans ranged from 21 to 43 years of age, averaging about 30 in all groups; campers ranged more widely in age, from seven to 68, but averaged 18 in the posthepatitis group and 23 in the heavily exposed. Medical students averaged 24 years of age.

A detailed *general medical history* obtained at the time of the examination was supplemented by information available from preëxisting medical records and from the Cornell Medical Index.[13] Specific inquiry was made into possible exposure to hepatitis virus and other sources of liver injury.

Information was obtained concerning alcoholic intake and nutritional status. The presence of functional overlay, when noted, was recorded. Evidence of specific episodes of liver disease, at any point in the history, was evaluated, particular attention being paid to the occurrence of jaundice and to laboratory confirmation. Finally, on the basis of the history alone, the examiner rated each individual as to relative strength of any suggestion of liver disease at follow-up.

A complete *physical examination* was made, with special attention to signs suggestive of liver disease, e.g., jaundice, "spider" nevi, palmar erythema, testicular atrophy, gynecomastia, liver enlargement and tenderness, splenomegaly, ascites, edema and other signs of portal hypertension. The physical findings at follow-up were also evaluated by the examiner as to the strength of any suggestion of liver disease, major emphasis being placed upon the presence and degree of jaundice, hepatic enlargement or tenderness, spider nevi, and signs of portal hypertension.

Laboratory studies included nonspecific tests as well as those directed toward detection of hepatic disturbance. *Nonspecific tests* included a complete blood count, routine urinalysis, serologic test for syphilis, and erythrocyte sedimentation velocity (Wintrobe). *Hepatic tests* routinely performed were: (1) total and prompt direct reacting (1′) serum bilirubin (TSB, 1′SB); (2) urine urobilinogen determination on both two hour and 24 hour specimens, employing the quantitative Ehrlich reaction for the former and the more specific extraction procedure for the latter; (3) cephalin cholesterol flocculation test, with readings after 24 and 48 hours (C24/C48); (4) thymol turbidity and flocculation tests, using a reagent buffered at pH 7.8 (T30/TF); (5) sulfobromophthalein retention (BSP), measured 45 minutes after 5 mg. per kilogram dose based on actual weight. The methods employed in this laboratory have been described elsewhere.[14]

Some or all of the following tests also were carried out on many persons: (1) serum protein with albumin-globulin fractionation by "salting out" technics and by electrophoresis; (2) prothrombin activity; (3) zinc sulfate turbidity (ZT) test for estimation of serum gamma globulin (Kunkel); (4) serum colloidal red (Ducci) and colloidal gold (Maclagen) tests; (5) serum alkaline phosphatase; (6) total serum lipid turbidity (phenol turbidity—Kunkel); (7) total per diem urinary coproporphyrin excretion (Watson and Schwartz).

Needle biopsy of the liver was performed on 11 patients with sufficient objective evidence of hepatic disturbance to justify the procedure.

Results of History and Physical Examination

Even *prior to the reference point* the medical *history* of the *veterans* was complex. All had experienced skin puncture, and many of the heavily exposed and the posthepatitis cases had already had malaria, viral pneumonia and gastrointestinal diseases. Prior to the epidemic of virus IH hepatitis,

the histories of the *campers* were comparatively free of major illness and were comparable to those ordinarily obtained from civilian groups of similar age and above-average economic status.

During the interval between the reference point (see above) and the time of the follow-up examination, *the frequency of "major episodes"* * of liver illnesses was of special interest. Among all 1,618 individuals (minimally exposed, heavily exposed and posthepatitis cases) studied by the *three* centers, there were 63 persons with 74 such episodes; in 91% of the episodes there was jaundice and in 16% there was laboratory confirmation. In the Philadelphia series of 615 persons with adequate information, 23 had had such major episodes, and the proportionate incidence was, by final survey diagnosis, for both veterans and campers combined:

Posthepatitis	21/269 (7.8%)
Heavily exposed	0/137 (0%)
Minimally exposed	2/209 (1.0%)

These differences reflect a pattern of recurring liver disease in some of the posthepatitis cases. However, if one assumes all such episodes in posthepatitis cases to be recurrences, and calculates recurrence rates for successive intervals after the original onset of hepatitis, one finds that the rate of "recurrence" is a markedly decreasing function of time. For all 746 posthepatitis cases studied in this way by the three centers, the rates at which major episodes occurred in succeeding years after onset are:

Years after Onset of Hepatitis	Major Episodes per 100 Men per Year
1	4.8
2	2.0
3	1.6
4	0.8
5 or more	0.6

The decline is marked and, although the rate of 0.58 episode per 100 men per year for the fifth and subsequent years still exceeds that of 0.13 calculated for the 872 minimally and heavily exposed individuals similarly studied, the rapidly falling rates are more suggestive of the subsidence of a disease process than of the emergence of an underlying, chronic one. That at least some major episodes among the posthepatitis cases are probably unrelated to the original hepatitis infection is shown by two campers in whom we ourselves observed major episodes (previous virus IH infections), and concluded that one represented a new infection with virus SH hepatitis and the other an attack of infectious mononucleosis, both with jaundice.

In reviewing the history and physical examination at follow-up, *the general health status* of the medical student controls was found to be definitely superior to that of the minimally exposed veterans from the NRC allocation,

* A "major episode," as defined herein, is an episode not continuous symptomatically or objectively with the reference illness (see text), in which the patient had definite jaundice for more than one day or was hospitalized for liver disease.

most notably in regard to symptoms but also in regard to tenderness of liver on percussion. These findings were reflected in differences between the two groups in laboratory results, as will be seen below. In view of their less complex medical histories, their greater youth, their comparative economic advantage, and their educational selection for good health, the medical students were regarded as poor controls for the heavily exposed and the posthepatitis veteran groups. A more complex problem concerns the form

TABLE 2

Comparisons between Posthepatitis and Control Groups as to Prevalence at Follow-up of Symptoms Consistent with Liver Disease, Separately for NRC Veterans and Campers

Symptoms	Posthepatitis		Heavily Exposed Minimally Exposed		P*
	No. of Cases Studied	% with Symptoms	No. of Cases Studied	% with Symptoms	
NRC Veterans					
CMI score >2+†	83	63.9	117	32.5	<.01
G.I. symptoms	123	62.6	192	42.7	<.01
Sexual symptoms	121	0	192	1.6	>.05
Strength and endurance symptoms	122	55.7	192	38.5	<.01
Summary of history:					
At least suggestive evidence of liver disease	126	57.9	192	38.5	<.01
At least strongly suggestive evidence of liver disease	126	1.6	192	.5	>.05
Campers					
G.I. symptoms	141	42.6	45	31.1	.11
Sexual symptoms	141	0	45	0	—
Strength and endurance symptoms	141	25.5	45	4.4	<.01
Summary of history:					
At least suggestive evidence of liver disease	144	34.0	46	21.7	.09
At least strongly suggestive evidence of liver disease	144	.7	46	.6	>.05

* Probability that the percentage figure for the posthepatitis group exceeds that for the control group by only a chance amount.

† More than 2 positive answers to G.I. questions (omitting questions 49 and 50) on Cornell Medical Index. The mean scores of 3.69 for the posthepatitis group and 2.06 for for the controls also differ significantly (P about .02).

of the comparisons of the three veteran groups: posthepatitis, heavily exposed and minimally exposed. Since one hypothesis shaping the sampling plan is that subclinical infections may carry a definite risk of residual liver damage, one would prefer to make comparisons on all three groups simultaneously and to pay careful attention to the pattern into which the three groups fall in each case. Actually, in the joint study of data from all three centers this complex procedure was followed. Here, however, a simpler

procedure may be adopted by first pursuing the hypothesis that subclinical infections carry a risk of residual injury.* For this purpose we first compared the 100 NRC minimally exposed veterans and 92 NRC heavily exposed veterans on all the details of history and physical examination. In all, 15 comparisons were made without finding a single significant discrepancy between them. It was therefore concluded that, at the level of the history and physical, there was no evidence that *subclinical* infections produced later liver damage, and that the possible effect of *clinical* infections with jaundice was best explored in the veterans by comparing posthepatitis cases with the

TABLE 3

Comparisons of Posthepatitis and Control Groups as to Prevalence at Follow-up of Signs Consistent with Liver Disease, Separately for NRC Veterans and Campers

Sign	Per cent of NRC Veterans with Sign			Per cent of Campers with Sign		
	Post-hep.	Heav. Exp. + Min. Exp.	p*	Post-hep.	Heav. Exp.	p*
Enlarged liver	6.3	9.4	>.05	5.6	2.2	>.05
Palpable liver	16.7	18.8	>.05	27.3	15.2	>.05
Liver tenderness on palpation	8.2	2.1	.01	3.6	4.3	>.05
Liver tenderness on percussion	9.0	5.8	>.05	1.4	0.0	>.05
Splenic enlargement	1.6	.5	>.05	0.0	2.2	>.05
Splenic tenderness	1.6	0.0	>.05	0.0	0.0	—
Jaundice, questionable	4.0	1.0	>.05	2.8	8.7	>.05
Spiders	7.1	3.1	>.05	4.2	4.3	>.05
Abnormal body hair pattern	0.0	0.0	—	1.4	0.0	>.05
Other skin abnormalities	12.0	19.3	>.05	9.2	4.5	>.05
Gynecomastia	0.0	0.0	—	0.0	0.0	—
Testicular atrophy	0.0	0.0	—	0.0	0.0	—
Edema or clubbed fingers	.8	.5	>.05	0.0	0.0	—
Summary of the physical:						
At least suggestive evidence of liver disease	12.7	9.4	>.05	8.4	6.5	>.05
At least strongly suggestive evidence of liver disease	3.2	2.1	>.05	0.0	0.0	—
Number of cases in each comparison	122 to 126	189 to 192		139 to 145	44 to 46	

*Probability that the percentage shown for the posthepatitis group exceeds that shown for the control group by only a chance amount.

heavily and minimally exposed groups combined. For the campers, comparisons were made between the posthepatitis and the heavily exposed groups.

On the basis of information obtained in the *history,* posthepatitis cases clearly manifest an excess of the vague, nonspecific symptoms that may occur with persistent liver disease. Table 2 provides a summary of the underlying comparisons; additional comparisons were made after omitting

* Neither the subclinical nor the posthepatitis groups would include those in whom a definite diagnosis of hepatitis without jaundice had been made.

cases with functional overlay and with evidence of nonhepatic disease,* with the same general results. One would hesitate to draw from this material any conclusion about the long-term effects of viral hepatitis, despite the large and statistically significant differences exhibited. The relatively high frequency of *symptoms* in the groups with *no* history of clinical hepatitis indicates that factors other than previous hepatitis play a major rôle in the prevalence of symptoms. Also, the observed differentials between the posthepatitis and the other groups are at very different levels in the veterans and the campers; at least suggestive evidence of liver disease (based on symptoms alone) was noted in 58 and 39% in the veterans, and in 34 and 22% in the campers. Finally, as shown below, there is little correlation between history and physical findings.

None of the persons subjected to *physical examination* during the survey presented overt jaundice, massive enlargement of liver or spleen, or signs

TABLE 4

Correlation between Examiner's Summary Evaluations of Signs and Symptoms as to Presence of Hepatic Disease at Follow-up, All Survey-groups Combined

Evaluation of Physical	Evaluation of History			
	Negative	Suggestive	Strongly Suggestive	Total
Negative	286	171	1	458
Suggestive	15	26		41
Strongly suggestive	1	2	2	5
Positive clinical diagnosis of liver disease		2	1	3
Total	302	201	4	507

of portal hypertension. Also, none of the signs suggestive of liver disease was seen frequently *in any one group*. Table 3 provides a summary of all the comparisons which were made. Among the veterans, liver tenderness on palpation was the only sign which was observed significantly more often † in the posthepatitis group than in the controls, while among the campers no significant differences were found. A single finding of significance (at the .01 level) in a series of 26 independent statistical tests has a chance probability of about .3. Our comparisons are not all independent in the strict sense, but they are nearly so, and it seems clear that the one instance of significance found here will not support a conclusion that the physical examination differentiated posthepatitis cases from others. Among those examined, only three individuals were classified by examiners as having physical evi-

* "Nonhepatic disease" is a term used here to denote the presence of other important disease which is not primarily hepatic.

† Throughout this paper differences are summarily dismissed as "not statistically significant" only if they are so small that the probability exceeds .05 that chance alone would produce differences as large or larger.

TABLE 5

Bromsulphalein Retention Results

Survey Group	Number Tested	Mean Value	Standard Error of Mean	Retention of at Least 10 Per Cent	
				Number	Per Cent
NRC minimally exposed	94	4.6	.3644	6	6.4
NRC heavily exposed	90	5.2	.3487	8	8.9
NRC posthepatitis	119	5.3	.4654	12	10.1
NRC—total	303	5.1	.2382	26	8.6
Local minimally exposed*	123	3.7	.1936	3	2.4
Local heavily exposed†	28	4.1	.4158	0	0
Local posthepatitis†	103	3.3	.2106	3	2.9
Local—total	254	3.6	.1351	6	2.4

* Medical students
† Campers

dence of liver disease when seen. Two (one an alcoholic) were among the veteran controls and one was among the veteran posthepatitis (IH) cases. The latter appeared to be in the active stage of acute hepatitis (type uncertain) at the time of the survey, and apparent complete recovery ensued within the usual period of recovery from an average attack of acute hepatitis.

Not only do the examiner's summary evaluations of both signs and symptoms fail to distinguish posthepatitis from the two control groups, but also these two summary judgments themselves are not highly correlated. Table 4 presents the detail of the relationship, which may be expressed quantitatively by the fourfold correlation coefficient $+.18$. Only 5% of those with a negative history were rated at least suggestive of liver disease on physical examination, in contrast to 16% of those with at least a suggestive history. Alternatively, only 38% of those with a negative physical were rated positive on history, in contrast to 67% of those with positive physical.

TABLE 6

24-Hour Urine Urobilinogen Results

Survey Group	Number Tested	Mean Value	Standard Error of Mean	Excretion of at Least 3 mg./100 ml.	
				Number	Per Cent
NRC minimally exposed	83	1.08	.1621	5	6.0
NRC heavily exposed	66	.98	.1542	5	7.6
NRC posthepatitis	99	.97	.1223	6	6.1
NRC—total	248	1.01	.0835	16	6.5
Local minimally exposed	132	.98	.0904	6	4.5
Local heavily exposed	36	.36	.0667	0	0
Local posthepatitis	95	.79	.1429	5	5.3
Local—total	263	.83	.0700	11	4.2

Results of Laboratory Tests

The laboratory tests also provide no significant evidence of a greater incidence of hepatic disturbance in posthepatitis cases than in the minimally or heavily exposed groups. Tables 5 and 6 compare the groups with respect to Bromsulphalein retention and 24 hour urine urobilinogen excretion. It may be noted that in the laboratory comparisons, unlike those based on the history and physical examination, we have used the group of medical students as a minimally exposed group with which to contrast the two camp groups. The Bromsulphalein retention values are noteworthy in that they indicate a difference, not between the survey groups on the basis of exposure to hepatitis, but between the veterans and the local (non-veteran) groups. The proportion of definitely abnormal values (retention of 10% or more) is 8.6% in the combined veteran groups as compared with 2.4% in the com-

Table 7

Comparison of Laboratory Results for Local and NRC Cases

Laboratory Procedure	Survey Group	Baseline for Comparison	Number Tested	Deviation from Baseline*		P
				Number	Per Cent	
S. bilirubin (total)	Local	2 mg./	330	6	1.8	
	NRC	100 ml. or more	318	4	1.3	>.05
S. bilirubin (1′)	Local	0.2 mg./	329	5	1.5	
	NRC	100 ml. or more	318	5	1.6	>.05
U. Ehrlich units/2h	Local	1 unit or more	228	17	7.5	
	NRC		262	30	11.5	>.05
U. urobilinogen/24h	Local	3 mg./100 ml.	263	11	4.2	
	NRC	or more	248	16	6.5	>.05
Ceph. floc.-24h	Local	1+ or more	323	8	2.5	
	NRC		317	5	1.6	>.05
Ceph. floc.-48h	Local	1+ or more	321	24	7.5	
	NRC		310	21	6.8	>.05
Thymol turbidity	Local	2.5 units or	327	14	4.3	
	NRC	more (Maclagen U.)	318	11	3.5	>.05
Thymol floc.	Local	1+ or more	327	18	5.5	
	NRC		313	13	4.2	>.05
Bromsulphalein	Local	10%	254	6	2.4	
	NRC	or more	303	26	8.6	<.01
Serum protein	Local	6.5 gm. or	137	3	2.2	
	NRC	less	304	25	8.2	<.05

* Baseline for comparison for each test was established at a point on the distribution curve for each test which would be most likely to reveal any existing significant difference between two groups, rather than at a point presumed to distinguish between normal and abnormal for an individual for that test. The data on frequency of deviations from the baseline as so defined thus are not synonymous with the frequency of abnormal results for each test in these groups.

TABLE 7 (*Cont.*)

Laboratory Procedure	Survey Group	Baseline for Comparison	Number Tested	Deviation from Baseline		P
				Number	Per Cent	
Serum albumin	Local	Less than 4 gm.	136	1	0.7	
	NRC		304	22	7.2	<.01
Serum globulin	Local	4 gm. or more	136	3	2.2	
	NRC		304	8	2.6	>.05
A/G ratio	Local	Less than 1	136	0	0.0	
	NRC		304	8	2.6	>.05
Prothrombin time	Local	Less than 70%	33	15	45.5	
	NRC	of normal	77	9	11.7	<.01
Zinc turbidity	Local	5 units or more	248	7	2.8	
	NRC		316	26	8.2	<.05
Colloidal red	Local	1+ or more	328	22	6.7	
	NRC		308	25	8.1	>.05
Colloidal gold	Local	1+ or more	256	16	6.3	
	NRC		259	7	2.7	>.05
Alkaline phosphatase	Local	8 units or more	122	18	14.8	
	NRC		262	9	3.4	<.001
Lipid turbidity	Local	30 units or more	71	8	11.3	
	NRC		309	22	7.1	>.05
Coproporphyrin	Local	1.6 microgm. per ml.	243	17	7.0	
	NRC	or more	190	28	14.7	<.05

bined local groups. The value of the chi-square corresponding to this difference is 8.74 (on one degree of freedom), $P < .01$. Similarly, although here the differences are not statistically significant, the 24 hour urobilinogen results differ more between veterans and non-veterans than between those with and those without prior hepatitis.

Similar comparisons have been made *for each of 19 laboratory procedures employed* and, since comparisons between survey groups were made separately for the groups of local and of NRC origin, there were 38 opportunities for differences between the survey groups to appear. One would expect, employing a 5% criterion of statistical significance, that about two of the 38 tests would turn out to be significant by chance alone. Actually this happened only once: among 142 (civilian non-veteran) posthepatitis cases, 15 (11%) showed at least 2 plus colloidal red reactions, whereas of 186 local minimally exposed persons only five (2.7%) showed more than questionable reaction. The corresponding difference was not observed among the NRC allocated cases, however, and it seems reasonable to dismiss this difference as a chance occurrence. On the other hand, differences between the local and NRC (veteran) groups are found frequently (table 7). Significant differences are found for seven of the 20 tests and, while these

tests are interrelated, there is no doubt that there are real differences between the groups.

Those revealing significant differences were: Bromsulphalein retention, total serum protein, serum albumin, prothrombin, zinc turbidity, alkaline phosphatase and urinary coproporphyrin excretion. The total protein undoubtedly is a reflection of the difference in the albumin factor. As might be expected, the more frequent abnormalities were found in the "NRC" group except for prothrombin and alkaline phosphatase. The difference in alkaline phosphatase probably is due to the fact that the local group includes many in the adolescent age group (from the camper group). Results from these were not compared separately with respect to normal criteria for this age group, and this probably accounts for the difference observed. The reason for the excess of prothrombin abnormalities in the camper group is not apparent. It is noted that the numbers tested were small in both groups,

TABLE 8

Evaluation of "Routine" Hepatic Tests
The Laboratory Score

Test	Normal	Suggestive	Strongly Suggestive	Positive	
	Score 0	Score 1	Score 2	Score 3	Score 4
TSB	<1.10 mg. %	1.10–1.35	1.36–2.5	2.6–6.0	6.1–18.0
1'SB	<0.21 mg. %	0.21–0.27	0.28–0.50	0.51–1.0	1.1–5.0
UB	0	1+	2+	3+	4+
UU/24°	<1.6 mg. %	1.6–2.09	2.10–3.0	3.1–4.5	>4.5
C24	0	±	1+	2+, 3+	4+
C48	0; ±; +	2+	3+	4+	
T30	<2.0 units	2.0–2.4	2.5–3.5	3.6–5.0	5.1–8.0
TF	0; +	1+	2+	3+	4+
BSP	<7.0%	7.0–8.7	8.8–12.0	12.1–18.0	18.1–25.0

particularly in the "local" group. Although the observed difference is highly significant, it is believed that this difference may be due to selection.

Inasmuch as the laboratory tests, considered individually, fail to distinguish the posthepatitis groups from the minimally and maximally exposed, ways were sought of combining the information provided by different tests in order to achieve greater sensitivity. This was done in two ways: by means of a "laboratory score" and by means of a generalized "t-test";[15] the latter tests whether two groups can be reliably distinguished by means of a suitably weighted linear combination of test results.

The laboratory score was created by assigning a score from zero to four to the results of each of the individual "routine" hepatic tests and adding the results together. Table 8 shows for each test the range of values assigned to each score. The "equivocal" rating (score 1) was assigned to the range of mean-plus-two standard deviations to mean-plus-three standard deviations as determined among the local controls (medical students). The range above the equivocal, considered to be abnormal or "positive," was

arbitrarily divided into three portions, to which were assigned the values 2, 3 and 4, representing progressively increasing degrees of deviation from the normal. The cephalin cholesterol flocculation test rating was taken to be the mean rating for the 24 hour and 48 hour readings if both were obtained. Thymol turbidity readings are in terms of the Maclagan unit, which is about one-half of the Shank-Hoagland unit.

While these tests may be influenced by factors other than hepatic disease, abnormal responses with any of these tests are considered suggestive of hepatic disease or disturbance when otherwise unexplained. Case V-210 (described below) illustrates that slight elevation of the 24-hour urine urobilinogen excretion alone, in the presence of normal results with all of the other tests, may represent evidence of significant liver disease. Unfor-

TABLE 9

Laboratory Scores

Laboratory Score	NRC Cases			Local Cases		
	Minimally Exposed	Heavily Exposed	Post-hepatitis	Minimally Exposed	Heavily Exposed	Post-hepatitis
	Number Scored					
Total	75	62	84	106	22	65
0	48	43	48	80	17	42
1	10	5	13	13	2	8
2	10	6	9	4	1	6
3	3	3	7	3	1	2
4 or more	4	5	7	6	1	7
	Per Cent Scored					
1 or more	36.0	30.6	42.9	24.5	22.7	35.4
2 or more	22.7	22.6	27.4	12.3	13.6	23.1
3 or more	9.3	12.9	16.7	8.5	9.1	13.8
4 or more	5.3	8.1	8.3	5.7	4.5	10.8

tunately, some of these tests presented certain difficulties and were not performed on all subjects. We have therefore assigned laboratory scores only to those persons for whom results were available for all eight tests which contribute to the score.

Table 9 shows the laboratory scores for the six survey groups. While the posthepatitis groups exhibit slightly higher scores than the minimally or heavily exposed groups, the differences are not statistically significant.

For the generalized t-test, laboratory results employed were: zinc and lipid turbidity, Bromsulphalein retention, alkaline phosphatase, total serum bilirubin, 24-hour urine urobilinogen and serum protein tests. The results were entirely negative. Although differences again were found between local cases and those allocated by the NRC, no significant differences could

be demonstrated between the posthepatitis cases and the minimally exposed groups.

It should be noted that the laboratory results, although apparently unrelated to the presence or absence of a history of hepatitis, were on the whole in good agreement with the elements of the history and physical examination. This was especially true of three tests: Bromsulphalein retention, zinc turbidity and the albumin-globulin ratio. The correlations of the A/G ratio were duplicated by correlations of the albumin and globulin fractions separately, but not by the total serum protein. Table 10 shows in summary form the statistically significant relationships. As might be expected, in

TABLE 10

Summary of Statistically Significant Relationships between Selected Clinical Observations and Laboratory Tests. Male Patients Only

	Bromsulphalein Retention			Zinc Turbidity			Albumin/ Globulin Ratio		
	N	$\bar{X}$	P	N	$\bar{X}$	P	N	$\bar{X}$	P
Symptoms in interval to follow-up									
Gastrointestinal	223	5.0	<.05	222	3.1	<.01			
Strength and endurance	169	5.2	<.01	168	3.1	<.05			
Findings at follow-up									
Nonhepatic disease	32	7.3	<.01	34	3.7	<.01	28	1.5	<.01
High alcohol consumption							50	1.6	<.01
Overweight	114	6.0	<.01	115	3.4	<.01	116	1.7	<.01
Liver enlargement	19	6.5	<.05	18	3.6	<.05			
Liver tenderness on percussion	20	6.8	<.01	20	4.2	<.01	18	1.5	<.01
Examiner's opinion of general health				39	3.8	<.01			
At least suggestive evidence of liver disease									
Based on history only	187	5.3	<.01	184	3.2	<.01			
Based on physical examination only	44	6.5	<.01	43	3.6	<.01	38	1.6	<.05
All men tested	550	4.6		551	2.9		423	1.8	
Standard deviation		3.4			1.4			.5	

every instance in which a relationship between A/G ratio and a clinical observation was found, the A/G ratio was depressed. Few of the differences in mean value are strikingly large; usually a few individuals with a stated physical finding have markedly elevated test results (e.g., eight of the 32 individuals with nonhepatic disease at follow-up have Bromsulphalein retention values of 10% or more), but the effect is also typically reflected by an apparent small shift in the results for many other individuals. Thus, in the example cited above, if all Bromsulphalein results of 10% or more are excluded, the mean retention value for 28 men with other diseases is 4.2%, while the mean retention for 490 men without any recognized disease is 3.9%.

The relationship of overweight to disturbance in Bromsulphalein results perhaps is not surprising, as the test dosage of dye was based on weight in these studies. However, the state of overweight is also significantly associated, not only with elevation of zinc turbidity and depression of the A/G ratio, but also with elevation of 24-hour urobilinogen excretion, and lipid turbidity.

Other clinical observations which were reflected by statistically significant, albeit small, alterations in laboratory results were:

1. *Strength and endurance alterations* in the interval from reference point to follow-up: associated with elevation in 24-hour urine urobilinogen, Bromsulphalein, thymol flocculation, zinc turbidity, coproporphyrin and gamma globulin; and with depression of alkaline phosphatase.

2. *"Nonhepatic" disease at follow-up:* associated with elevation of Bromsulphalein retention, zinc turbidity, direct bilirubin and serum globulin, and with depression of the serum albumin and the A/G ratio.

3. *Tenderness of liver on percussion:* associated with elevated Bromsulphalein retention, thymol turbidity, zinc turbidity, and globulin and decreased albumin and A/G ratio.

4. *History suggestive of present liver disease:* associated with elevated Bromsulphalein, thymol turbidity, zinc turbidity, serum protein, urinary coproporphyrin, direct bilirubin and decreased alkaline phosphatase.

5. *Physical examination suggestive of present liver disease:* associated with elevated Bromsulphalein retention, thymol turbidity, zinc turbidity, and serum globulin; with decreased A/G ratio and abnormal colloidal red.

The Nature of Demonstrated Hepatic Disturbance as Revealed by Liver Biopsy

In this study, 11 persons were considered to have sufficient objective evidence of hepatic disturbance to justify needle biopsy of the liver. All had positive laboratory scores, although the history and physical findings were variable. The importance of histologic examination of liver tissue in the interpretation and evaluation of data obtained in surveys of this type is clearly indicated by the following cases:

Case Reports

Case V-210. W. B., a 27 year old Negro male of the "veteran posthepatitis" group, had two years of Army service in the Pacific (1943–45). During 1944 he had both dengue fever and malaria. During the following year, as indicated by Army medical records, he had hepatitis with jaundice and infection with *Schistosoma japonicum.* In 1948, after his release from service, diagnoses of infectious mononucleosis and of syphilis were made. For the latter he was given a 10-day course of penicillin.

He reported for follow-up examination in March, 1949. At that time he complained of easy fatigue, intermittent nausea, and occasional arthralgia and myalgia. Physical examination was negative except for moderate bilateral cervical adenopathy.

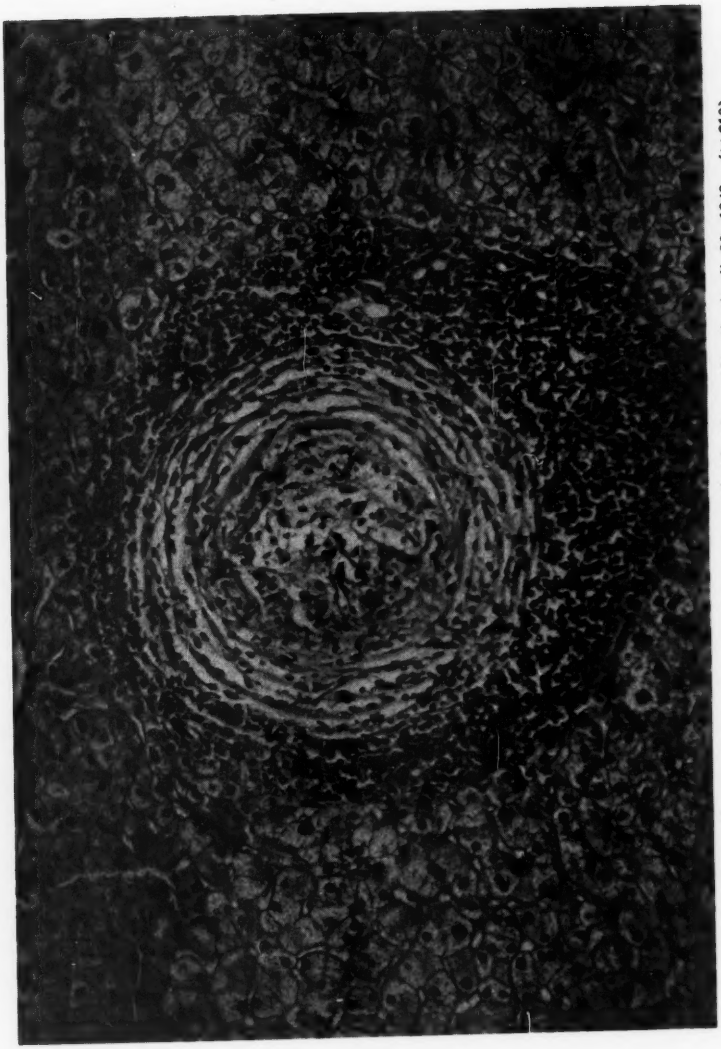

FIG. 1. Photomicrograph, needle liver biopsy, Case V-210, biopsy No. 1, April 23, 1949; (×210).

Routine hepatic tests revealed as the *only* abnormality a slight elevation of the 24-hour urine urobilinogen excretion (3.71 mg.). This was confirmed by repetition of the tests, the urine urobilinogen excretion again being very slightly elevated (2.57 mg./24 hours).

Needle biopsy of the liver was performed by one of us (J. R. N.) on April 23, 1949. Microscopic examination of the specimen (figure 1) was reported by Dr. William Ehrich as follows:

"The outstanding feature of this biopsy is the presence of a well circumscribed granuloma in a periportal space. The core of the granuloma consists of epithelioid cells. These are surrounded by a wide ring of thick hyalinized collagen fibers. The latter are surrounded by a zone of densely crowded lymphoid cells and eosinophils.

"The liver cells are well preserved but contain abundant sudanophilic and iron-positive pigmented granules. The periportal spaces are essentially normal. The sinus endothelial cells are loaded with fat.

"Comment: The granuloma does not look like a tubercle or gumma but is more likely to be due to a tropical disease such as schistosomiasis."

Case V-53. A. B., a 40 year old white male of the *"veteran heavy exposure"* group, had three years of Army service in the Pacific (1942–45). In November, 1945, shortly after his release from service, with discontinuance of Atabrine, he had an attack of malaria followed by five recurrences. His medical history otherwise was not remarkable except for possible periods of dietary inadequacy. No illness suggestive of hepatitis was recalled. Since childhood he had abstained from eating meat because of personal convictions, although fish and dairy products were not excluded. Because of this voluntary elimination of meat and all meat products from the diet, his diet may have been inadequate at times during his period of Army service.

He reported for a follow-up examination in August, 1948. He had no symptoms and considered himself to be in excellent health. Physical examination revealed a stocky, well nourished male weighing 168 pounds (height, 64 inches). The edge of the liver was just palpable, but was not thought to be significantly enlarged or tender. No other significant physical findings were detected. The results of the routine hepatic tests were all normal except for the Bromsulphalein retention of 14.5% after 45 minutes. Persistent elevation of Bromsulphalein retention was noted on each of two subsequent examinations, values of 16% and 17% being obtained.

Needle biopsy of the liver was performed by one of us (J. R. N.) on September 23, 1948. Microscopic examination of the specimen (figure 2) was reported by the late Dr. Tracy B. Mallory as follows:

"The liver shows focal, very coarse fat vacuolization. This is probably on a nutritional basis. There is no evidence of present or past hepatitis.

"Diagnosis: Focal fat vacuolization."

Case V-129. N. P., a 37 year old white male of the *"veteran heavy exposure"* group, had 18 months of Army service in Italy during 1944 and 1945. In August, 1944, he was hospitalized for 10 days with an illness officially diagnosed as "acute catarrhal enterocolitis." At that time he had mild diarrhea and temperature elevations up to 105° F. He had no nausea, vomiting or jaundice. He was unable to recall any change in the color of his urine or stools. The duration of this illness was approximately two weeks.*

He reported for follow-up examination in October, 1948. His only complaints at that time were easy fatigue of mild degree, of six to eight months' duration, and intermittent mild periumbilical discomfort apparently unrelated to food. Physical

* On the basis of the information available to us, the possibility that this illness represented acute hepatitis without jaundice cannot be excluded.

FIG. 1. Photomicrograph, needle liver biopsy, Case V-210, biopsy No. 1, April 23, 1949; (×210).

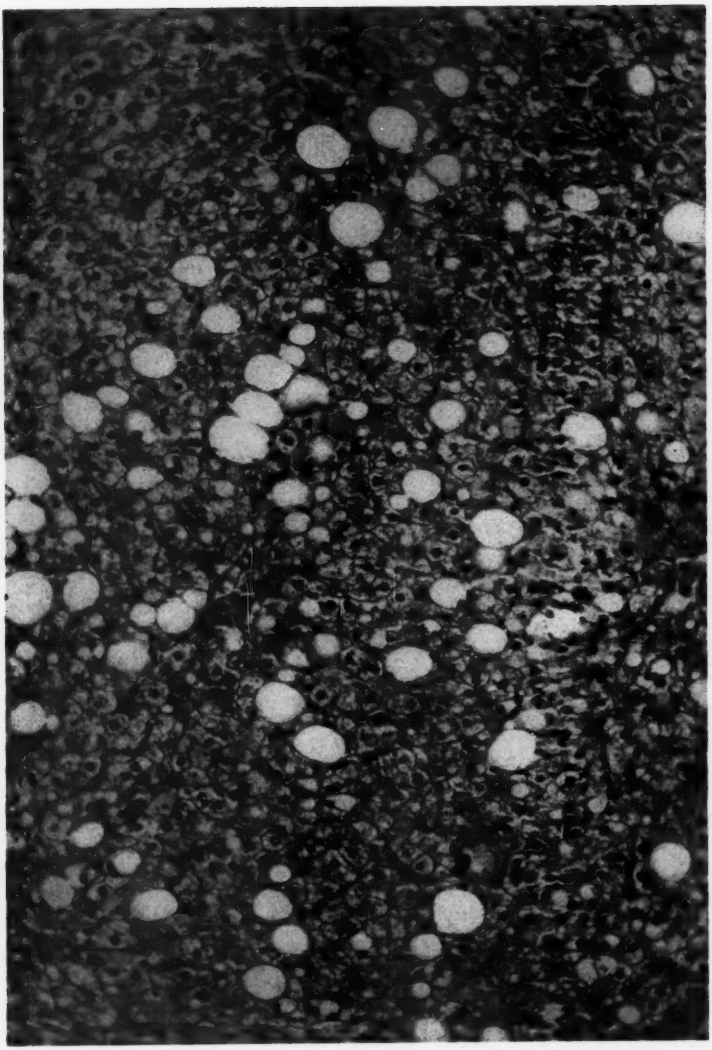

FIG. 2. Photomicrograph, needle liver biopsy, Case V-53, biopsy No. 1, September 23, 1948; (×210).

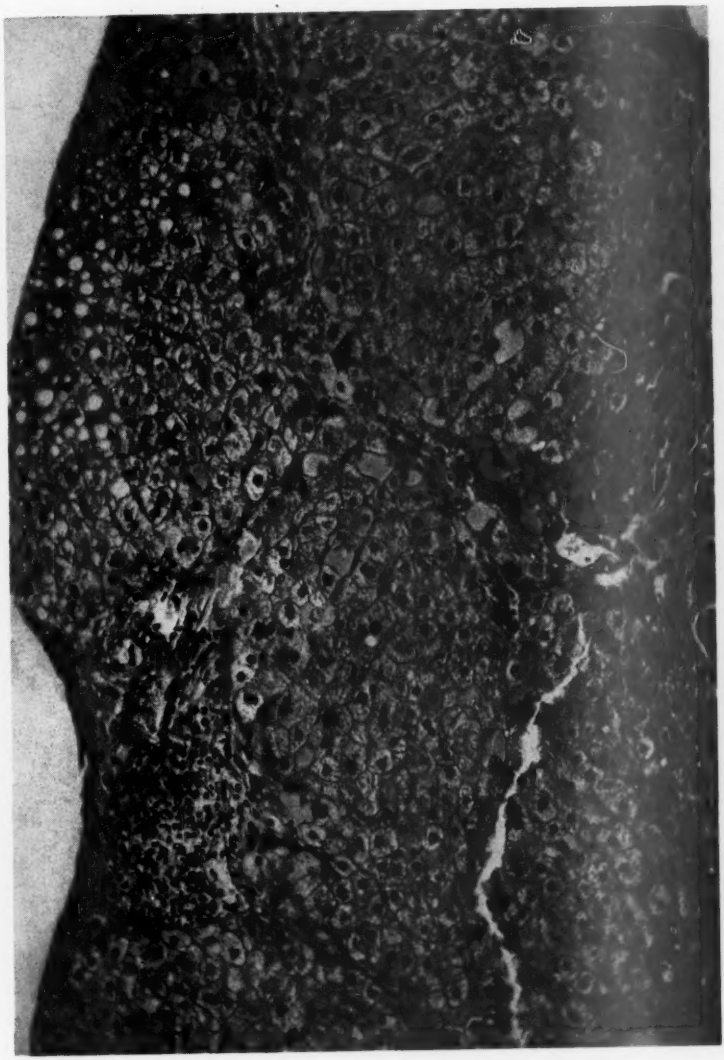

FIG. 3. Photomicrograph, needle liver biopsy, Case V-129, biopsy No. 1, February 10, 1949; (×200).

FIG. 2. Photomicrograph, needle liver biopsy, Case V-33, biopsy No. 1, September 23, 1948; (×210).

examination was negative. The routine hepatic tests revealed definite abnormalities, including positive cephalin, thymol and Bromsulphalein tests, the latter becoming increasingly more abnormal over a period of seven months although the serum bilirubin was never elevated. During this interval no significant change in symptoms or physical findings was noted.

Needle liver biopsies (figures 3 and 4) were obtained by one of us (J. R. N.) on February 10, 1949, and on May 26, 1949. Microscopic examinations of these specimens by Dr. William Ehrich were as follows:

"The patient has a serious and progressive liver disease.

"In February, 1949, the liver showed considerable infiltration with mesenchymal cells of the portal tissue. Most of the cells were mononuclear cells with small dark nuclei; others were fibroblasts; a few were eosinophils. There was some increase in the number and thickness of the collagen fibers. There was some destruction of the adjacent liver cells.

"The lobules showed swelling, particularly of the peripheral liver cells, with homogenization of their cytoplasm and considerable alteration of their nuclei. Some nuclei showed dissolution, others contained huge nucleoli, still others were large and hyperchromatic, and there were double nuclei present as well. Some of the cells contained large fat drops. There was no bile retention, no acidophilic necrosis.

"Now, on May 26, 1949, we find considerable progress of the disease. The portal fields are much larger; they are less cellular, but show more fibroblasts and abundant thick collagen fibers, and they also reveal some macrophages containing iron pigment and fine fat droplets. The adjacent liver cells show considerable destruction, a few reveal acidophilic necrosis.

"The lobules are now greatly altered. There are large streamers of large homogenized pink liver cells with hyperchromatic and pyknotic nuclei and there are now a good many nuclei with large nucleoli. A good many liver cells now contain fine iron-positive granules, and there is iron also in some Kupffer's cells. Fat stain reveals abundant, mostly fine fat droplets, especially in the central liver cells, and there is a good deal of fat also in the Kupffer's cells. Bile retention is not conspicuous. We also find scars scattered through the lobules.

"Diagnosis: Early liver cirrhosis? Chronic hepatitis?" This patient has been closely followed by one of us (J. M. G.) to date. From the time of follow-up study to January, 1953, his hepatic tests were consistently positive, varying only in degree. Two major episodes were experienced during the interval from follow-up to date. In November, 1952, he was placed on cortisone and improvement in the hepatic tests was noted promptly. Cortisone was continued for a 60-day period. Since January, 1953 his hepatic tests have been within normal limits.

Case V-247. T. R., a 22 year old white male of the *"veteran minimal exposure"* group, had had "physiologic" jaundice as a newborn but no history of jaundice since that time. During his short period of Army service (1945–46), all of which was confined to the United States, he was hospitalized on one occasion for a spontaneous pneumothorax. Recovery from this was uneventful, and his past medical history otherwise was not remarkable.

At the time of his follow-up examination in March, 1949, he had no symptoms and considered himself to be in excellent health. The edge of the liver was just palpable, but it was not thought to be significantly enlarged or tender. Physical examination otherwise was negative. The responses of the routine hepatic tests were all normal except for Bromsulphalein retention of 8% after 45 minutes. Two subsequent Bromsulphalein tests revealed 45 minute retention of 13% and 10.6%. The other hepatic tests again were normal on each of these occasions.

Because of the persistent elevation of Bromsulphalein retention, a needle biopsy of the liver was performed by one of us (J. R. N.) on April 30, 1949. Microscopic

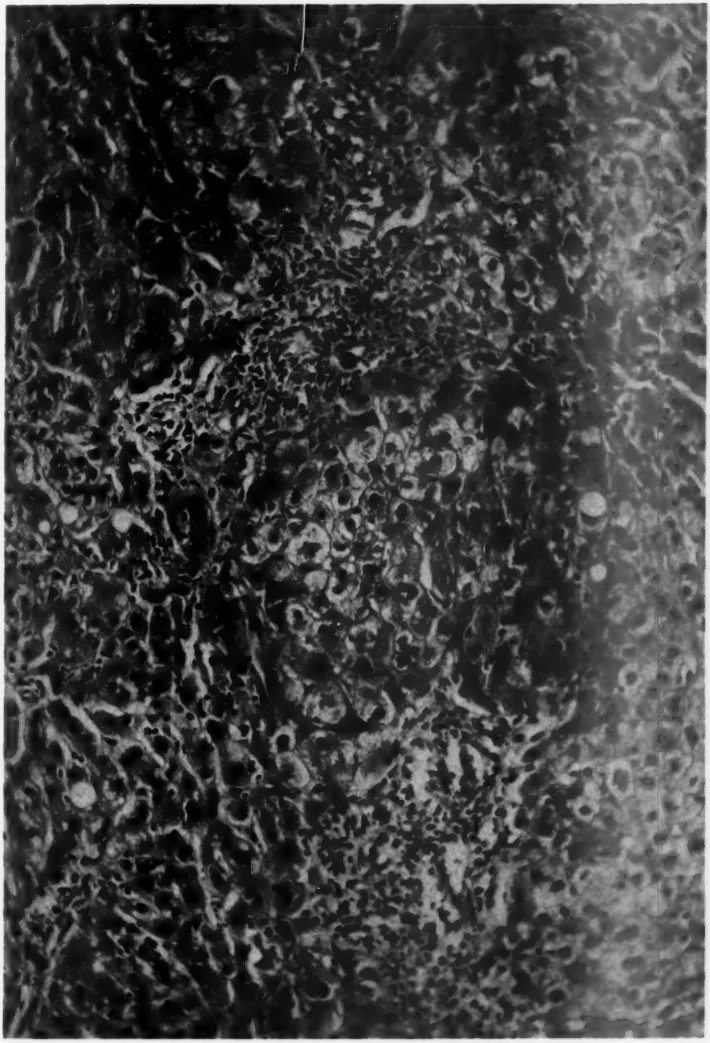

FIG. 4. Photomicrograph, needle liver biopsy, Case V-129, biopsy No. 2, May 26, 1949; (×185).

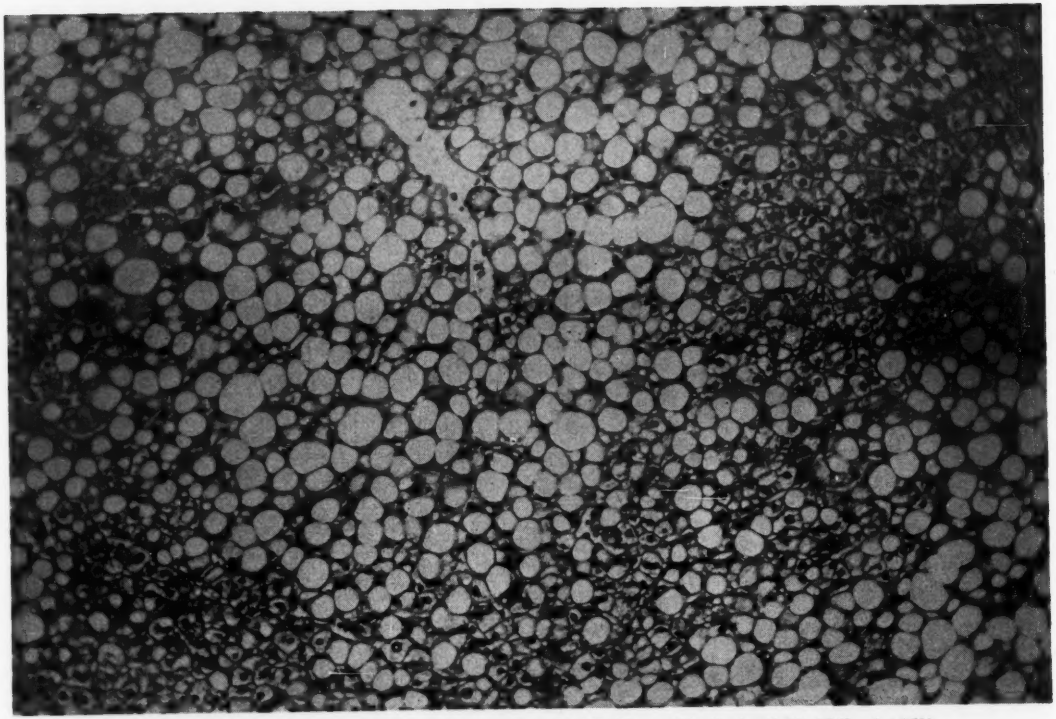

FIG. 5. Photomicrograph, needle liver biopsy, Case V-247, biopsy No. 1, April 30, 1949; (× 150).

examination of the specimen (figure 5) by Dr. William Ehrich was reported as follows:

"The outstanding feature of this biopsy is a marked fatty infiltration of the liver cells. There are huge fat drops, especially in the intermediary and central sections of the lobule. Some cells show large pathologic nucleoli in their nuclei. There is no obvious pigmentation, no bile retention, but some liver cells contain fine iron-positive granules. The periportal spaces show some thickening and hyalinosis of the collagen fibres in places but there is no increase in cellularity. No bile duct proliferation.

"*Diagnosis:* Fatty infiltration."

The patient continued to demonstrate elevated Bromsulphalein retention at approximately monthly intervals despite what appeared to be adequate lipotrophic therapy. In December, 1949, he contracted infectious mononucleosis and also demonstrated the typical changes in the hepatic tests. Because the hepatic tests persisted in the abnormal range, he was re-biopsied in January, 1950. The report was that of a subsiding hepatitis; no fat was present. Subsequent follow-up examinations revealed a return of all hepatic tests, including the Bromsulphalein retention, to normal.

Discussion

The difficulties involved in the interpretation of data obtained by this type of survey have become clearly apparent during the course of this analysis. The survey has provided laboratory evidence suggesting an incidence of some form of "hepatic disturbance" in at least 2% of apparently "healthy" persons who have had no previous known experiences with hepatitis viruses and, as indicated by the trend of findings in the "veteran minimal exposure" group, the incidence may be as high as 5% in certain groups who have had no recognized unusual exposure to hepatitis virus. In addition, recent studies of blood donors meeting the standard requirements indicate that approximately 11% have suggestive evidence of subclinical nonspecific "hepatic disturbance."[16] Further, in the present study a detailed analysis of the laboratory evidence provided both by individual tests and by groups of tests fails to demonstrate a statistically significant association of hepatic disturbance with a history of prior hepatitis. The only clear-cut differences were found between NRC allocations of representative veterans and locally acquired medical students and campers, not between groups defined on the basis of previous experiences with the virus of hepatitis. The histologic findings in the four cases reported herein revealed four different patterns of morphologic change, probably representing at least three different etiologic types of hepatic disease. Thus, in case V-210 representing the "veteran posthepatitis" group, the probable cause of the minimal hepatic functional disturbance leading to biopsy was found to be a granulomatous process rather than chronic hepatitis. In case V-129, representing the "veteran heavy exposure" group (no history of jaundice), the histologic changes were consistent with those of chronic hepatitis. In case V-53, representing the same group, the hepatic functional disturbance apparently was the result of a process characterized by a severe fatty meta-

Fig. 5. Photomicrograph, needle liver biopsy, Case V-247, biopsy No. 1, April 30, 1949; (×150).

morphosis. These observations clearly indicate the fallacy of attempting to draw conclusions concerning the nature of hepatic disturbance on the basis of clinical and laboratory evidence alone. Thus, the later presence of hepatic disturbance in a person who previously had viral hepatitis does not necessarily afford evidence of causal relationship. Likewise, the absence of a history of hepatitis with jaundice does not exclude previous infection with a hepatitis virus as the initiating cause of subsequent hepatic disturbance. Thus, histologic study of liver tissue appears to be absolutely essential for proper interpretation of survey data on the incidence and nature of specific types of hepatic disturbance. Unfortunately, even this information does not permit evaluation of the rôle of specific etiologic agents in all instances. For this reason, final conclusions concerning the relationship of previous hepatitis to the incidence of hepatic disturbance observed in the present groups seem to require information obtainable only by means of routine liver biopsy, plus specific tests for hepatic virus and other etiologic agents which are not yet available.

In spite of this limitation, the laboratory data obtained on the camp "posthepatitis" group strongly suggest that, under ordinary circumstances, an average attack of hepatitis followed by apparent recovery does not, in itself, lead to an increased incidence of hepatic disturbance which can be demonstrated four to eight years later. This suggests the possibility that the increased incidence * of hepatic disturbance in the *"veteran posthepatitis"* group, if real, may have been the result of the combined effect of hepatitis and certain predisposing or associated factors, plus a higher incidence of other etiologic types of liver injury resulting from the greater exposure of this group to a variety of agents and conditions that might result in liver injury. Additional biopsy studies will be required to evaluate the relative importance of these various factors.

During the course of this survey we have encountered no one with advanced chronic hepatic disease in whom the condition could be attributed only to preceding acute viral hepatitis with jaundice that initially was followed by apparent recovery. However, case V-129 may represent a form of chronic liver disease initiated by acute hepatitis (without jaundice). The incidence of such major sequelae following nonfatal acute viral hepatitis with jaundice thus would appear, on the basis of this study, to be very low. On the other hand, the incidence of mild hepatic disturbance, type undetermined, has been relatively high in all unselected groups, irrespective of their exposure to hepatitis virus. The nature and ultimate significance of such hepatic disturbance cannot be defined on the basis of the present study. It is hoped that the significance will be clarified by further study and continued observation over a period of years.

The structure of the present study permits the investigation of group differences in such fashion that certain of them might be attributed to the

* Not statistically significant.

effect of antecedent hepatitis, however difficult it might be to prove the etiology of a particular case of cirrhosis. However, at the level of the history and physical examination there is no real evidence of cirrhosis in any of the 271 cases studied here four to eight years after the onset of hepatitis. Moreover, a supplementary mortality study, based on an analysis of death certificates on deaths among 3,800 veterans with a history of hepatitis in World War II, has shown that their mortality rate from cirrhosis is not greatly in excess of expectation. In all, there were 44 observed veteran deaths, in contrast to the 55 expected on the basis of 1949 death rates for United States males, and there were three deaths from cirrhosis in contrast to the 0.76 expected. Although the latter discrepancy has a probability of about .04, two of the men who died of cirrhosis were alcoholics and in the third cirrhosis was diagnosed within six months of the onset of hepatitis. In any event, the discrepancy is so small as to indicate that the results of the present study are not modified by the loss through death, prior to the follow-up study, of a significant number of cases with fatal hepatic disease following acute hepatitis.

The thymol turbidity data reported herein were obtained by the use of the thymol reagent buffered at pH 7.8. Recent studies [17] have indicated that the thymol reagent buffered at pH 7.55 is more sensitive than that buffered at pH 7.8 and yields a higher incidence of abnormal results when applied to large groups. For this reason the thymol test performed with the reagent buffered at pH 7.55 would appear to be preferable for screening programs directed toward the detection of subclinical hepatic disturbance. The normal range for 24-hour urine urobilinogen excretion shown in table 8 is somewhat lower than that indicated in the literature.[18] However, the control subjects from which our "normal" criteria were derived were well screened, and the findings described in reference to case V-210 indicate that values elevated above our normal range, but not beyond that described in the literature, may be significant. Further studies of the normal per diem excretion of urine urobilinogen on well screened "normal" subjects would appear to be indicated for the purpose of establishing the range of normal urobilinogen excretion.

The results of the present study do not indicate that acute viral hepatitis with jaundice is incapable of initiating a chronic progressive hepatitis culminating in diffuse fibrosis, portal hypertension, advanced hepatic insufficiency and death. They do indicate that the incidence of such chronic liver disease initiated *solely* by acute hepatitis with jaundice is very low in males, in the age groups studied, within the four to six year follow-up period. Thus, the results of this study are valid only in this qualified sense. It is entirely possible that a similar study of the major sequelae of hepatitis in women, in older age groups, or in persons with other associated medical conditions or exposures would yield an incidence significantly different from that observed in the present study. Further, in the absence of routine histologic study of liver tissue it is impossible to draw conclusions regarding

the frequency, in posthepatitis patients, of a diminished hepatic reserve which is not revealed by abnormal hepatic tests, clinical symptoms or signs, but which may ultimately influence their longevity. Finally, none of these studies to date permits conclusions regarding the rôle of viral hepatitis without jaundice in the etiology of chronic liver disease. Perhaps of significance is the fact that the several proved long-term blood carriers of hepatitis virus with laboratory and histologic evidence of advanced chronic hepatic disease (cirrhosis) have had no history of an acute initial attack of hepatitis with jaundice.[19, 20] In the present study, and in those at the other two centers, the "posthepatitis" cases included, by selection, only those who had had jaundice, as it was believed impossible to obtain from Army records an adequate series of cases of hepatitis without jaundice in which the diagnosis could be accepted with reasonable certainty. Thus, although the maximally exposed and control groups may have included some such cases, a true picture of the effect of non-icteric disease is not available from this study. This is an important point, because many of the patients observed in clinical practice with chronic hepatic disease and cirrhosis of a type resembling a chronic hepatitis have evidence of a well developed chronic process by the time they are recognized and usually have no history of an initial icteric attack. Resolution of this question must await the development of specific tests for hepatitis virus which will perhaps clarify the relationship of this type of chronic liver disease to hepatitis virus.

Summary

The incidence and nature of hepatic disturbance have been investigated in: (1) "Posthepatitis" Group: 271 representative persons chosen from records containing sufficient information to justify a diagnosis of acute viral hepatitis with jaundice two to seven years previously; (2) "Heavy Exposure" Group: 138 representative persons chosen from records indicating unusual exposure to hepatitis virus during the preceding seven years; (3) "Minimal Exposure" Group: 242 persons selected because of the lack of any recognized unusual exposure to hepatitis virus. The study of each person included a detailed history, a complete physical examination, and a comprehensive group of hepatic tests. Needle biopsy of the liver was performed on 11 selected cases.

Of the tests generally available, and on the basis of the norms of this laboratory, the 24-hour urine urobilinogen excretion and the measurement of Bromsulphalein retention provided evidence suggestive of hepatic disturbance more frequently than any of the other "routine" hepatic tests employed.

Although the prevalence of nonspecific "symptom-complexes" was highest among the "veteran posthepatitis" group, the available data suggest that factors other than, or in addition to, the "hepatitis experience" are concerned in the figures for all groups.

The prevalence of physical and laboratory findings suggestive of hepatic disturbance also was highest in the "veteran posthepatitis" group. However, their prevalence in the other groups again indicated a probable influence of etiologic factors other than the "hepatitis experience" alone on the total figures.

On the basis of these data, the prevalence of laboratory evidence suggesting the presence of mild hepatic disturbance, without implication as to etiology, may be as high as 5% in certain groups of young adults who have had no recognized unusual exposure to hepatitis virus. The application of a *group* of properly selected hepatic tests is essential for the detection of subclinical hepatic impairment which may exist in the absence of symptoms and physical findings.

Histologic study of liver tissue obtained by needle biopsy from representative cases indicated the fallacy of drawing conclusions concerning the nature of demonstrated hepatic disturbance on the basis of prior history or current clinical and laboratory data alone. Thus, at least three presumably different etiologic types of hepatic disturbance, irrespective of the presence or absence of a previous history of hepatitis, were revealed among the 11 patients subjected to liver biopsy.

Of 651 persons studied, including 271 known to have had acute hepatitis with jaundice four to seven years previously, none has presented the physical or laboratory findings of advanced hepatic disease attributed solely to the "hepatitis" experience. One of the heavy exposure group who had an illness during military service diagnosed as enterocolitis, but which may have been hepatitis without jaundice, has presented laboratory and histologic evidence of a chronic hepatic disease compatible with chronic hepatitis associated with diffuse fibrosis, but the relationship to the original illness is uncertain as no interval observations are available between the reference illness and the follow-up examination. The few other individuals with evidence of chronic liver disease were not limited to the posthepatitis group, and all had additional etiologic factors which may have contributed to the hepatic injury (alcoholism, malnutrition, ulcerative colitis, etc.).

Conclusions

1. For males of the age groups studied here the prevalence of demonstrable severe or active chronic liver disease was not significantly higher in those with a previous history of hepatitis with jaundice than in those with no previous history of recognized hepatitis.

2. Etiologic factors other than, or in addition to, hepatitis appear to be responsible for the relatively high prevalence of mild hepatic disturbance, type undetermined, observed in all of the various groups studied. The nature and relative importance of these various factors in the prevalence of chronic hepatic disease remain to be determined.

3. The occurrence of chronic hepatic disease following acute viral hepa-

titis may depend on an association of hepatitis with other etiologic or predisposing factors related to the host and the environment.

4. Routine measurement of the 24-hour urine urobilinogen excretion and of Bromsulphalein retention, in addition to the other commonly employed hepatic tests, will increase the frequency of detection of subclinical hepatic disturbance.

5. The occurrence of an episode of liver disease more than three symptom-free years following an initial attack of hepatitis should make one consider the probability of a new infection or other process, rather than an exacerbation of the original disease.

6. In the absence of confirmation by histologic examination of liver tissue, definite conclusions concerning the relationship of previous hepatitis to subsequent hepatic disturbance may be misleading.

7. The present study does not provide information concerning the possible rôle of acute non-icteric viral hepatitis in the etiology of chronic liver disease, as all of the posthepatitis patients of this study had jaundice initially.

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Summario in Interlingua

Le apparente initiation de chronic morbo hepatic per acute disordines interpretate como acute hepatitis viral ha essite observate satis frequentemente pro justificar le conception que iste typo de infection es un causa potential de seriose e chronic morbo hepatic. Nonobstante, le exacte natura de iste relation—le frequentia con que chronic morbo hepatic es initiate per acute hepatitis viral e le factores responsabile pro iste supponite sequentia de evenimentos—ha nunquam essite ben definite.

Le presente reporto describe le resultatos de un studio comprehensive de iste problema. Le studio poteva esser interprendite gratias al disponibilitate de facilitates organisate per le Consilio National de Recercas (*National Research Council*) pro le observation post-tractamental de veteranos e altere gruppos pertinente. A causa del alte frequentia de hepatitis viral in le servicios militar in recente annos, nostre interprisa gaudeva del generose supporto del Administration de Veteranos (*Veterans Administration*).

De accordo con le plano general de studios recommendate per le Sub-Committee pro Morbos Hepatic intra le Consilio National de Recercas, le thema, "Frequentia e Cha-

racter de Disturbation Hepatic Sequente Acute Hepatitis Viral con Ictero," esseva investigate in 3 classes de subjectos: (1) Un gruppo "post-hepatitic"—continente 271 individuos representative, seligite super le base de protocollos con satis information pro justificar le diagnose de acute hepatitis viral con ictero a periodos de inter 2 e 7 annos passate. (2) Un gruppo a "exposition extreme"—continente 138 individuos representative, seligite super le base de protocollos indicative de grados inusual de exposition a viruses de hepatitis sed sin ulle traciabile attacco del morbo. E (3) un gruppo a "exposition minimal"—continente 242 individuos representative, seligite a causa del absentia in lor historia de ulle traciabile exposition inusual al virus de hepatitis.

Le studio de cata individuo includeva un historia detaliate, un complete examine physic, e un comprehensive serie de tests del functiones hepatic. Biopsias a agulia esseva executate in 11 seligite casos. Omne le datos assi accumulate esseva tabulate in un forma appropriate al analyse statistic. Iste analyse esseva interprendite, secundo un plano prearrangiate, per le statisticos consulente del Consilio National de Recercas. Super le base de lor resultatos le sequente conclusiones pare justificate:

1. In masculos del etates includite in nostre studio, demonstrabile casos de chronic morbo hepatic de forma sever o active non esseva significativemente plus alte inter le personas in qui le morbo pareva exclusivemente attribuibile al occurrentia de acute hepatitis con ictero a periodos de inter 4 e 7 annos passate que inter le personas in qui nulle previe attaccos de hepatitis esseva recognoscibile.

2. Factores etiologic altere que o in ultra de hepatitis es apparentemente responsabile pro le relativemente alte frequentia de leve disturbationes hepatic de indeterminate typos que esseva observate in omne le varie gruppos coperite per nostre studio. Le natura e le importantia relative de iste varie factores in le prevalentia de chronic morbo hepatic remane a determinar.

3. Le occurrentia de chronic morbo hepatic post acute hepatitis viral depende possibilemente del association de hepatitis con altere factores etiologic o predisponente in le individuo o in su ambiente.

4. Le mesuration routinari del diurne excretion urinari de urobilinogeno e del retention de bromsulfateina in conjunction con le altere tests hepatic de uso general, va augmentar le frequentia del detection de disturbationes hepatic de grado subclinic.

5. In casos del occurrentia de un episodio de morbo hepatic con un intervallo de plus que 3 annos sin symptomas post un attacco initial de hepatitis, on deberea considerar le probabilitate de un nove infection o un altere processo plus tosto que un exacerbation del disordine original.

6. In le absentia de verification per examines histologic del hepate, definite conclusiones in re le relation de previe attaccos de hepatitis con subsequente disturbationes hepatic pote esser erronee.

7. Le presente studio non provide information super le rolo possibile de acute hepatitis viral sin ictero in le etiologia de chronic morbo hepatic, proque omne le casos posthepatitic in le studio esseva casos con ictero.

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THE DIAGNOSIS OF ESOPHAGEAL CARCINOMA BY EXFOLIATIVE CYTOLOGY, INCLUDING TWO CASES OF CARDIOSPASM ASSOCIATED WITH CARCINOMA OF THE ESOPHAGUS *

By MELVIN I. KLAYMAN, M.D.,† *Chicago, Illinois*

DESPITE advances in radiology and endoscopy, the clinician is frequently confronted with the problem of a suspected but undetected esophageal carcinoma. Recent renewed interest in exfoliative cytology has indicated its clinical merit in establishing the presence of malignancy in accessible organs. However, its value for the diagnosis of esophageal lesions is not generally appreciated despite several earlier publications.[1, 2, 3] The purpose of this report is to emphasize further the high degree of accuracy and the contribution possible by this technic. In addition, case summaries of cardiospasm associated with carcinoma in two individuals (one unsuspected) and an unanticipated esophageal carcinoma are briefly presented.

METHOD

Patients were fasted for a minimum of eight hours prior to the test. A 1% Pyribenzamine gargle was used for oropharyngeal anesthesia. A Levin tube was passed through the mouth into the stomach whenever possible and the gastric content recovered was discarded. A Ringer's solution lavage was performed with processing of this material. The patient then sipped and swallowed 100 to 200 c.c. of Ringer's solution, which was recovered via the intragastric tube. The tube was withdrawn to the level of the cardia and irrigations were performed at various levels of the esophagus. If a persistent resistance was encountered in the esophagus during the passage of the tube, irrigations were conducted at this level. The collected material was immediately placed in plastic tubes, immersed in ice and centrifuged for three minutes within five minutes of aspiration. The sediment was smeared on glass slides and fixed in the standard alcohol-ether fixative. Rubin's modification of the Papanicolaou staining procedure [2] was used. Results were reported either as malignant cells present (indicating the cell type whenever possible) or not present.

Examinations were conducted on hospitalized and out-patients prior to x-ray and esophagoscopy, in several instances, without mishap. Fluoro-

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† Public Health Service Research Fellow of the National Cancer Institute, Department of Medicine, The University of Chicago.

scopic control was not required but was resorted to when an obstruction was found to identify its level, supplementing tube measurement. Patients found to have retained material were drained by an Ewald tube and lavaged until clear before testing. Foreign matter of any type usually invalidates the test, as the cellular material during centrifugation is then destroyed beyond morphologic identification. The average time required for study of each patient was 20 minutes, with the patient free to leave on completion.

Results

A total of 40 patients with suspected esophageal pathology were examined by the cytologic method. Twenty of these were shown to have malignant growths, as proved histologically in 18 and by the operative

Table 1

20 Malignant Lesions of Esophagus
(Esophagus 16, Cardia 4)

	Diagnosis			
	Malignant	Indeterminate	Nonmalignant	Incomplete
X-Ray (20)	13	4	3	2
Esophagoscopy (19)	15		2	
Biopsy (16)	12	1	3	
Exfoliative cytology (20)	19		1	

Table 2

20 Nonmalignant Lesions of Esophagus

	Diagnosis		
	Benign	Indeterminate	Incomplete
X-Ray (20)	18	2	2
Esophagoscopy (11)	9		
Exfoliative cytology (20)	20		

diagnosis of neoplasm in the remaining two. There were 20 patients with benign esophageal lesions, including cardiospasm, lye stricture, peptic ulceration with and without stricture, idiopathic stricture, congenital short esophagus, hiatus hernia, diverticula and motility disturbances. Tables 1 and 2 record the results of radiologic, esophagoscopic (with biopsies) and cytologic examinations. As the cytologic reports noted either the presence or absence of malignant cells, there were no "indeterminate" reports. Esophagoscopy was incomplete in four instances due to non-coöperation of one patient, kyphoscoliosis in two instances, and inability to pass the instrument beyond an obstruction presenting normal mucosa in one case. Two of these patients had carcinoma correctly diagnosed by cytology. The third patient disclosed

a benign stricture histologically. The single indeterminate esophagoscopic biopsy resulted from recovery of amorphous noncellular material. In two instances the first esophagoscopic biopsy was negative, with evidence of malignancy on a second examination. In both, the cytologic study correctly disclosed the malignancy present. There were no false-positive cytologic

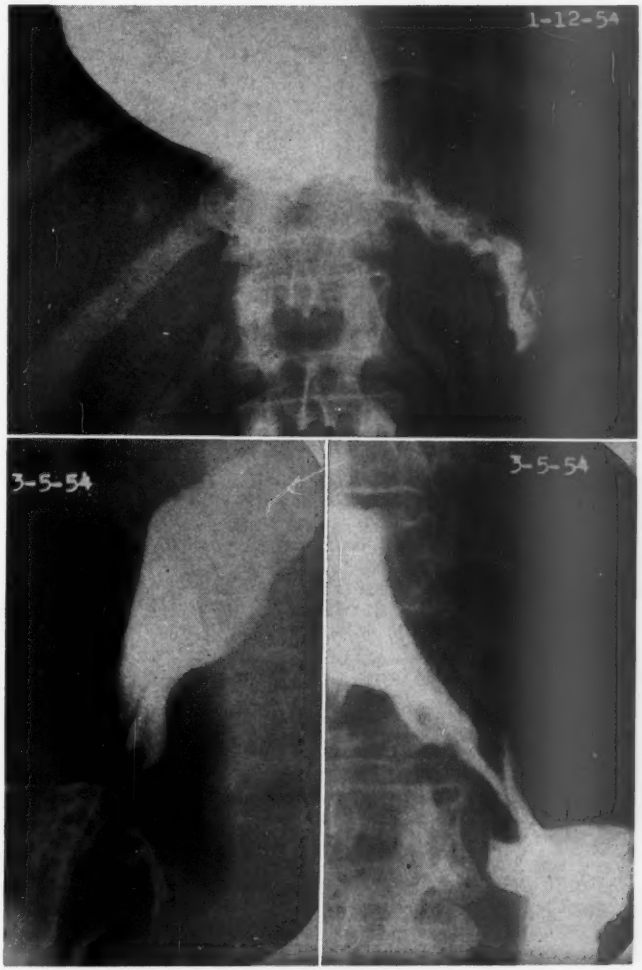

FIG. 1. X-ray views of the lower esophagus of case 1. January 12, 1954: The esophagus terminates in a symmetric narrowing; the ragged deformity beyond is interpreted as in the stomach. March 5, 1954: Two views taken following dilatations of the cardia.

reports. The single malignant case misdiagnosed by cytology proved to have an intact mucosal surface except for a minute fissure covered by a membrane, with carcinomatous penetration into the wall. This circumstance reflects the basic limitation of this technic; exfoliation of malignant cells into the lumen is necessary if the cells are to be recovered.

During the course of this study, three cases demonstrated clearly the contribution of exfoliative cytology in detecting unsuspected malignancy of the esophagus. Brief case summaries follow.

Case Reports

Case 1. A 55 year old female had been well until five years prior to entry, when she noted dysphagia and epigastric pain. She consulted her family physician and the x-rays were interpreted as cardiospasm, no malignancy. She had intermittent

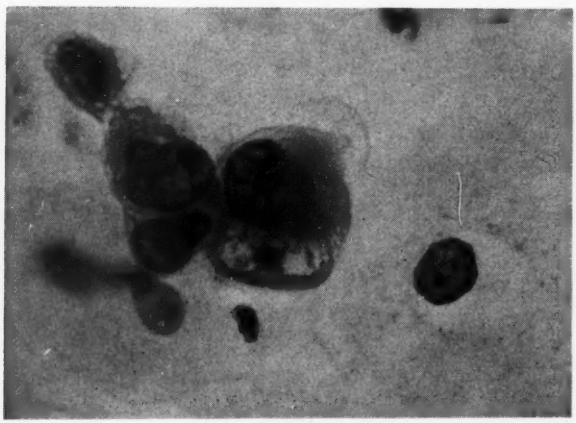

Fig. 2. Exfoliated squamous carcinoma cells. (× 950.)

episodes of this difficulty at meal time but then would be symptom-free for long periods of time. Three years previously, following "stomach flu," she noted dysphagia, vomiting and a weight loss of 30 pounds for a two week period. Since then she had continued with intermittent attacks of dysphagia and vomiting (many self-induced to relieve the pain and fullness). In recent months she had noted pain in the mid and left epigastrium. There was no history of hematemesis, melena or recent weight loss.

Physical examination disclosed a well nourished female, not appearing acutely or chronically ill, with essentially normal findings. Laboratory results: hemoglobin, 15.5 gm. per 100 c.c.; red blood cells, 5.1 million; hematocrit, 44%; white blood cells, 5,900, with a normal differential. Urinalysis, normal. Stools, negative to benzidine on three occasions. X-ray studies (figure 1, 1–12–54) revealed cardiospasm, with a hugely dilated esophagus containing an air fluid level at the level of the clavicle. X-rays of the chest, colon, terminal ileum and gall-bladder were normal. At esophagoscopy the esophagus was markedly dilated. At 33 cm. from the upper teeth a

localized area of swollen hemorrhagic mucosa was seen and biopsied. The cardiac area was folded several times but a bougie was easily passed into the stomach. The cardia dilated easily with a bougie, French No. 26. Impression: (1) cardiospasm with mega-esophagus; (2) localized pathologic area at 33 cm., biopsied. The biopsy demonstrated hyperplastic stratified squamous epithelium, no malignancy. After seven dilations, unequivocal squamous cell carcinoma was found in the exfoliated cells (figure 2). Because of the cytologic diagnosis of malignancy, reëvaluation of the case was undertaken. A second roentgenographic examination (figure 1, 3–5–54) reported marked improvement in the appearance of the esophagus as compared with the previous examination. The second esophagoscopic examination recorded the area at 35 cm. as less inflamed than earlier, and it was biopsied. The cardiac sphincter area was friable and bled easily, presumably due to the dilatations. The instrument was easily passed into the stomach. The biopsies from two suspicious areas disclosed hyperplastic stratified squamous epithelium at 35 cm. and squamous cell carcinoma at the cardia (figure 3). At operation, the lower esophagus was distended and a hard, 5 by 10 mm. nodule apparently located in the wall was found at the esophagogastric junction. At about 8 cm. from the cardia a huge tumor located on the right side of the esophagus began and extended upward beyond the aortic arch. This tumor was hard and did not encircle the organ. A few lymph nodes were involved in the right side of the mediastinum, one of which revealed squamous cell carcinoma. The lesion was considered inoperable and was treated by radiation therapy. The condition of the patient has gradually deteriorated with the passage of time.

Comment: In this instance, exfoliative cytology was the *only* diagnostic method which identified the malignancy. Although an esophageal carcinoma present since the onset of symptoms cannot be disproved, the clinical course of this patient does not conform to that of the majority of cases.

This case is unusual from other aspects also. The interval of five years from onset until the discovery of malignancy is considerably shorter than previous reports of carcinoma developing in patients with cardiospasm. Baer and Sicher [4] reviewed this problem and found that the shortest period from onset of dysphagia was 10 years. Vinson [6] stated in 1942 it was his belief that when carcinoma is found at the cardia in patients with cardiospasm the original lesion is the carcinoma. The prevalent theory for the formation of malignancy in cardiospasm is that of Rake,[6] who postulates that retained saliva and food in the dilated lumen promote bacterial growth, resulting in an acute esophagitis which progresses to a chronic stage, with formation of shallow ulcers; with attempts at regeneration, warty growths or definite papillomata develop. As the irritation continues, malignancy may result. The resultant intraluminal carcinoma is in the middle third of the esophagus.[4, 7–11] This case does not conform to this concept. It would appear that this patient suffered from either cardiospasm with an atypical type of malignant degeneration or a malignancy from the onset, a "chronic carcinoma" of the esophagus, simulating cardiospasm.

Case 2. A 68 year old male complained of mild, intermittent dysphagia, with food sticking at the xiphoid area, for the past 15 to 20 years. Four years earlier he had been hospitalized elsewhere because of increasing dysphagia. Cardiospasm was diagnosed and treated by dilatations, with relief of symptoms. Three months before entry he had noted the return of dysphagia, more marked than previously and

FIG. 3. A biopsy of the cardia showing squamous cell carcinoma with exfoliating cells from the surface. (×450.)

FIG. 3. A biopsy of the cardia showing squamous cell carcinoma with exfoliating cells from the surface. (× 450.)

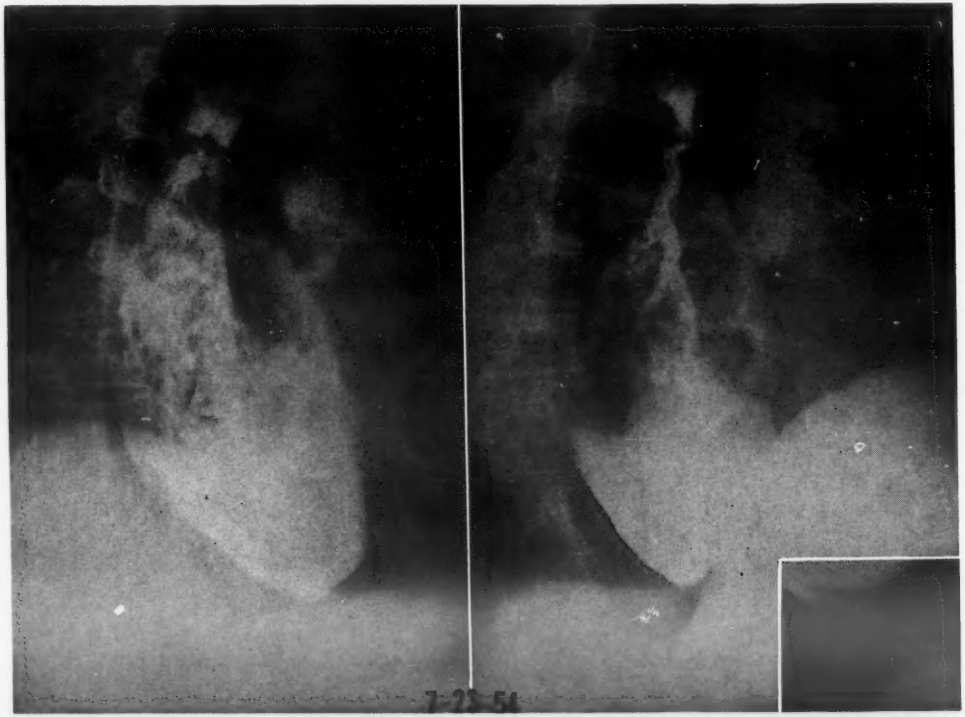

FIG. 4. Two views of the dilated esophagus of case 2, with the symmetric narrowing of the cardia in the inset.

associated with a fear of eating (he vomited the undigested food six to 12 hours postprandially), a cough which was aggravated by food, a substernal and left scapular pain noted at night, and a weight loss of 28 pounds. No hematemesis or melena had been observed. Diabetes mellitus had been recently discovered. Physical examination disclosed an emaciated elderly male appearing chronically ill. Laboratory studies: hemoglobin, 12.3 gm. per 100 c.c.; red blood cells, 3.56 million; hematocrit, 37%; white blood cells, 10,600, with 80 polymorphonuclear leukocytes, 19 lymphocytes and 1 monocyte. Urinalysis, 4 plus reduction. Stool, 4 plus benzidine. Total protein, 5.9 gm. per 100 c.c., with 3.4 gm. per 100 c.c. albumin and 2.5 gm. per 100 c.c. globulin. Four sputum smears for acid-fast bacilli, negative. An esophageal x-ray examination was reported as cardiospasm with marked atony and dilatation of the esophagus (figure 4). A large fibrocalcific lesion in the right lung apex, probably tuberculous, was reported by the roentgenologist. At esophagoscopy marked dilatation and retention in the lower one-half of the esophagus were observed. Exfoliative cytology demonstrated squamous cell carcinoma cells (figure 5). Because of the cytologic

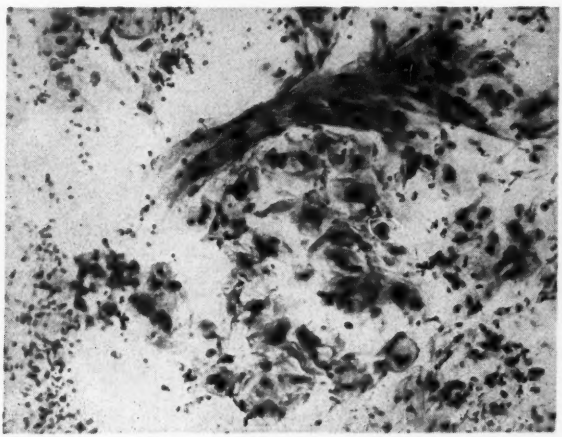

FIG. 5. Groups of exfoliated squamous carcinoma cells. (× 160.)

finding, a second esophagoscopy was performed. At 24 cm. from the incisors the mucosa became thickened and friable, and this extended to the lower end of the esophagus. Impression: extensive mural carcinoma of the esophagus. Two biopsies exhibited squamous cell carcinoma. To prepare for definitive surgery the patient underwent a gastrostomy, at which time an abdominal exploration revealed no evidence of tumor. During the initial postoperative period he did well, but his condition deteriorated with the development of pulmonary difficulty. He died on the twenty-first postoperative day.

At postmortem examination a large, fungating, ulcerating carcinoma was observed in the middle third of the esophagus, extending into the periesophageal tissues and the mediastinum. The tumor measured 14 by 12 cm. and almost completely encircled the esophagus; there was a tracheo-esophageal fistula with perforation into the right main stem bronchus. Histologically, the lesion was a squamous cell carcinoma. The remainder of the esophagus disclosed an intense degree of leukoplakia

and dilatation above and below the tumor. Bilateral aspirative bronchopneumonia and bilateral healed apical tuberculosis were noted. The recent gastrostomy site appeared in good condition, with no infection or leakage of gastric contents.

Comment: Although malignancy was suspected clinically, the first objective evidence of its presence was gained by cytology. In view of the previous comments, it should be noted that this case conforms classically to the recorded cases of cardiospasm associated with carcinoma.

Case 3. A 69 year old male complained of anorexia, tiredness, jaundice and a weight loss of eight pounds of two weeks' duration. Two years earlier he had first noted an intolerance for fatty foods. Examination at that time disclosed an enlarged liver. For 18 months he had noted a substernal burning pain, relieved by eating. X-rays taken elsewhere three days before entry suggested an infiltrating gastric ma-

FIG. 6. The gross specimen of case 3 showing the 2.5 by 1.7 cm., oval ulcerating carcinoma in the mid-esophagus, and a lymph node involved with metastatic malignancy (arrow).

lignancy. Physical examination disclosed a chronically ill, jaundiced male with hepatomegaly. Laboratory results: hemoglobin, 13.5 gm. per 100 c.c.; red blood cells, 3.71 million; hematocrit, 45%; white blood cells, 10,550. Urinalysis showed bile and urobilinogen present. Gastric analysis revealed achlorhydria. Liver functional tests suggested hepatocellular and obstructive abnormalities. A normal esophagus and stomach were reported by the radiologist. At gastroscopy no malignancy was observed. Malignant cells (squamous carcinoma cells and questionable adenocarcinoma cells) were found in the cytologic study of gastric aspirates. At exploration no gross malignancy was found. A liver biopsy was interpreted as a possible primary bile duct carcinoma. The patient did poorly following surgery and died on the third postoperative day.

Postmortem examination revealed an acute, massive necrosis of the liver. A 2.5 by 1.7 cm. oval, ulcerating, poorly differentiated squamous cell carcinoma was found in the mid-esophagus with metastases to the mediastinal lymph nodes (figure 6).

Comment: This patient presented the problem of the differential diagnosis of jaundice. The malignant cells obtained by cytologic examination were interpreted as arising either from the esophagus or from a bile duct carcinoma. In view of the absence of esophageal symptoms and negative x-rays, a bile duct carcinoma was considered most likely. It is noteworthy that malignant cells were recovered from an unanticipated carcinoma of the esophagus. Although asymptomatic, the patient had developed metastases to the mediastinal nodes.

Discussion

From these observations it would appear that exfoliative cytology can detect carcinoma of the esophagus accurately and in instances where radiology and esophagoscopy fail. The known limitations of radiology and esophagoscopy for the diagnosis of early esophageal carcinoma are well recognized. It is in this area that exfoliative cytology holds great promise in recovering malignant cells before disturbance of motility or other gross abnormalities can be observed. Thus, by earlier diagnosis, it may be possible to attain the desired goal of increased "patient cures."

There appears to be an increased incidence of malignant degeneration of the esophagus in cardiospasm. As the symptoms of this condition simulate carcinoma, the clinician may be lulled into a false sense of security after establishing the initial diagnosis. Further recurrences of symptoms, typical or atypical, may be considered as part of the natural history of the benign disease. Thus the early malignancy is overlooked and recognized only too late for effective therapy. Therefore, exfoliative cytology should be performed annually and with each exacerbation of symptoms in patients with cardiospasm in addition to radiographic and esophagoscopic examinations for the detection of malignancy.

Summary

Forty patients in whom esophageal pathologic lesions were suspected were examined cytologically by lavage with Ringer's solution via a Levin tube. Nineteen of 20 cases with malignancy were correctly diagnosed by exfoliative cytology. There were no false-positive reports. Of the 20 benign lesions, all were correctly reported on the basis of cytologic examinations. The results of radiology and esophagoscopy with biopsies are compared with those of exfoliative cytology. Brief case summaries of cardiospasm associated with esophageal carcinoma in two patients (one unsuspected) and of an unanticipated esophageal carcinoma are reported. The clinical value of exfoliative cytology in the esophagus is briefly discussed.

Acknowledgment

Grateful acknowledgment is made to Miss Sylvia Pleticka for technical assistance, and to Dr. Walter L. Palmer and Dr. Joseph B. Kirsner for their support of this study.

Summario in Interlingua

Le meritos clinic de cytologia exfoliative in le detection de crescentias maligne in organos directemente accessibile es un facto establite. Nonobstante, le valor de iste methodo in le diagnose de lesiones esophagee non es generalmente recognoscite e require un re-assertion special.

Un serie de 40 patientes sub suspicion de pathologia esophagee esseva examinate per medio de lavage a solution de Ringer via un tubo del typo Levin. In 20 casos crescentias maligne esseva demonstrate histologicamente e al operation. Secundo examines roentgenologic, 13 casos esseva maligne, 4 indecise, e 3 non-maligne. Secundo examines esophagoscopic, 15 casos esseva maligne, 2 non-maligne, e in 2 casos le examine non esseva completate. Biopsias esophagee indicava lesiones maligne in 12 casos e lesiones non-maligne in 3 casos; un specimen esseva indecise. In 2 casos le prime biopsia esophagee esseva negative, sed evidentia de malignitate esseva trovate al secunde examine. Cytologia exfoliative detegeva malignitates in 19 casos. Le sol caso non detegite per iste methodo habeva un superficie mucosal completemente intacte con le exception de un minute fissura coperite per un membrana. Iste observation pote servir a signalar le limitationes fundamental del methodo.

In 20 casos le lesiones esseva considerate como benigne. Illos includeva nulle caso con un erronee reporto de malignitate basate super le examine cytologic.

Durante le curso del presente studio, 3 casos rendeva distinguite testimonio del valor de cytologia exfoliative. Illos es brevemente reportate.

Caso 1.—Le patiente esseva un femina de 55 annos de etate. Cinque annos antea un diagnose de cardiospasmo habeva essite basate super examines clinic e radiologic. Al recurrentia del symptomas le diagnose de cardiospasmo esseva corroborate per investigationes roentgenographic, per esophagoscopia con biopsia, e per essayos laboratorial. Nonobstante, le exfoliate squamose cellulas carcinomatose obtenite per aspiration esophagee indicava le presentia de un malignitate. Un re-evalutation del datos colligite e le subsequente intervention chirurgic confirmava le existentia del carcinoma.

Caso 2.—Le patiente esseva un masculo de 68 annos de etate. Durante le passate 15 a 20 annos ille se habeva plangite de dysphagia intermittente. Quatro annos retro le diagnose de cardiospasmo habeva essite establite. Le recurrentia del symptomas insimul con emaciation motivava un nove studio del caso. Le examine radiographic corroborava un diagnose de cardiospasmo, e le esophagoscopia monstrava pronunciate dilatation e retention in le medietate inferior del esophago. Cytologia exfoliative demonstrava maligne squamose cellulas carcinomatose. Un secunde examine esophagoscopic revelava le presentia de un carcinoma parietal. Plus tarde isto esseva confirmate per biopsia.

Caso 3.—Le patiente esseva un masculo de 69 annos de etate. Ille monstrava nulle symptomas esophagee sed marcate ictero e hepatomegalia. Le reporto roentgenographic indicava esophago e stomacho normal. Le stomacho appareva normal etiam sub gastroscopia. Cellulas maligne esseva constatate per cytologia gastric. Illos esseva (1) cellulas del typo squamose e (2) questionabile cellulas adenocarcinomatose, considerate como originari del esophago o del ducto biliari. Le exploration abdominal monstrava nulle grosse malignitate. Le examine post morte revelava un massive necrosis acute del hepate e un ulcerante carcinoma esophagee de forma oval con dimensiones de 2,5 e 1,7 cm. Metastases habeva occurrite al nodulos lymphatic mediastinal.

Iste observationes pare indicar que cytologia exfoliative pote accuratemente deteger carcinomas del esophago, mesmo in casos in que radiologia e esophagoscopia ha fallite. In vista del crescente frequentia de maligne degenerationes esophagee in casos de cardiospasmo, cytologia exfoliative—supplementante examines radiographic e esophagoscopic—deberea esser executate in omne patientes cardiospasmodic, omne anno e in plus con omne exacerbation del morbo, a fin de assecurar le prompte detection de nove malignitates.

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LOCALIZED BRONCHIECTASIS SIMULATING PULMONARY NEOPLASMS*

By BENJAMIN SCHWARTZ, M.D., *Brooklyn, N. Y.*, and HARRY L. KATZ, M.D., *New York, N. Y.*

WITH progressively wider utilization of routine chest roentgenograms, an increasing number of intrathoracic lesions is being discovered in asymptomatic persons. Once these abnormal pulmonary shadows are visualized radiologically it becomes the responsibility of the clinician to evaluate the nature of the pulmonary lesion in order that the proper therapy may be promptly instituted. Among the varied lesions that may be revealed by routine chest radiography, the isolated and circumscribed pulmonary densities often present elusive and challenging problems in diagnosis. The diagnostic studies required in such cases include the following:

1. A complete medical history. This should include a detailed review of all respiratory complaints, a history of past malignant disease, and previous travel or residence in endemic areas for histoplasmosis and coccidioidomycosis. Frequently the patient will seek medical advice because of a variety of complaints, such as cough, expectoration, hemoptysis, dyspnea, wheezing, recurrent respiratory infections and temperature elevations. In other instances symptoms may be insignificant or entirely absent, and the abnormal chest roentgenogram may be the only clue to the presence of pulmonary disease.

2. A complete physical examination and a careful fluoroscopic examination of the chest.

3. Roentgenographic studies. These should include, in addition to the conventional films, those special views, such as lateral, oblique, lordotic and overpenetrated exposures, employing the Potter-Bucky diaphragm, which may be required for better localization and more detailed delineation of the pulmonary lesions. Tomography is useful for revealing calcification or cavitation which may not be apparent on routine film exposures, and for demonstrating the anatomic pattern of adjacent bronchi.

4. Sputa and gastric examinations for acid-fast bacilli and fungi, as well as cytologic examinations of sputum or bronchial washings for malignant cells by the Papanicolaou staining technic. Although these examinations are usually indicated, it must be recognized that negative reports may not solve the problem, especially if the lesion is peripherally located.

5. Skin tests with tuberculin, histoplasmin, coccidioidin and blastomycin. These should be carried out on all patients displaying solitary pulmonary densities on roentgen films.

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From the Pulmonary Clinic, Veterans Administration Regional Office, Brooklyn, N. Y., and the Chest Section, Veterans Administration Hospital, Brooklyn, N. Y.

6. Bronchoscopic examination. Although this procedure is generally also performed more or less routinely, it will be of little value in the diagnosis of a peripheral lung lesion.

7. Aspiration biopsy. This is advocated by some in those cases where other diagnostic studies have been noncontributory. Most clinicians are of the opinion that this procedure can be successfully employed only when the pulmonary lesions are relatively large, and that its routine use is not warranted because of the many hazards associated with this method.

8. An exploratory thoracotomy. This is usually considered unavoidable when the diagnosis remains obscure in spite of the employment of the measures enumerated above. Certainly there is general agreement that one of the worst practices is merely to observe the patient in order to see whether the density will enlarge or change in configuration on serial roentgenograms.

The literature on the subject of isolated pulmonary lesions is too extensive to permit a detailed review.[1-4] It is noted, however, that bronchography has only infrequently been recommended as a significant procedure in the diagnosis of solitary pulmonary masses. The diagnostic value of bronchography in such conditions is usually considered to be the demonstration of obstruction of smaller bronchi or distortion of the bronchial tree by a peripherally placed pulmonary neoplasm.[5, 6] If these were the only positive findings to be looked for, a bronchographic examination would indeed not be of great assistance in the diagnosis of circumscribed pulmonary disease, since this would merely reveal graphically that a mass either impinged upon or displaced the bronchi in its vicinity. Moreover, this information can usually be demonstrated quite effectively by tomography. It is the purpose of this report to point out that not infrequently bronchography may establish the nature of a pulmonary nodule or mass by depicting graphically that it represents an area of localized bronchiectasis. In some cases the bronchiectasis may be limited entirely to the segment occupied by the pulmonary shadow. In other instances bronchography will display, in addition, bronchiectatic dilatations of variable extent in other parts of the same or opposite lung, the existence of which had not been suspected from the appearance of the routine chest films.

Review of the literature disclosed few reports of localized bronchiectasis as a clinical entity.[7, 8] In none of the recorded cases did the ordinary chest roentgenogram reveal significant abnormalities. Bronchography was performed because of the persistence of distressing respiratory systems, and established the diagnosis. We wish to emphasize that localized bronchiectasis, whether symptomatic or nonproductive of respiratory symptoms, may at times be manifested on the ordinary chest films as well circumscribed densities simulating pulmonary neoplasms.

Material

We have observed this phenomenon in six cases, each of which presented a somewhat different diagnostic problem. It is of interest that in three cases

the circumscribed pulmonary densities were revealed initially on survey chest radiography. In the remaining three cases the pulmonary shadows were discovered following diagnostic studies undertaken because of complaints referable to the respiratory system. However, the diagnosis of localized bronchiectasis had never been established prior to bronchography in any of these cases.

Reports of four illustrative cases of this group follow:

Case Reports

Case 1. In January, 1951, following a routine employment chest roentgenogram, this 26 year old white male was informed that he had a "spot" in his left lung. Periodic roentgenograms were taken at three month intervals thereafter until January, 1952 when he was advised to seek hospitalization because of changes in the roentgen appearance. He was admitted to the Brooklyn Veterans Administration Hospital on April 25. His only complaint on admission was a mild, chronic cough, productive of a small amount of mucoid sputum, which had been present since childhood. He

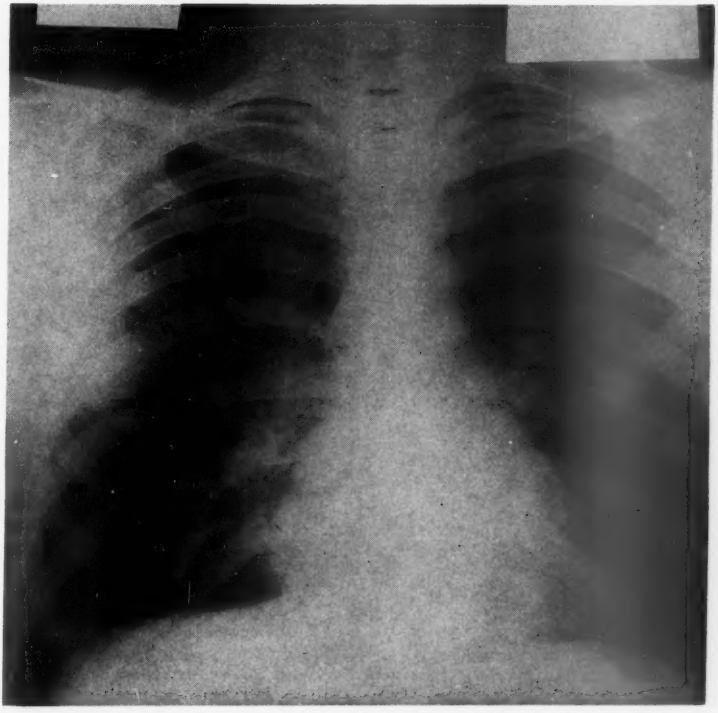

Fig. 1. *Case 1.* Chest roentgenogram taken on September 10, 1951, shows a circumscribed mass about 5.5 cm. in diameter in the right mid-lung field, and a discrete, nodular density about 2.5 cm. in diameter in the left mid-lung field.

had experienced two episodes of "virus pneumonia" since 1948, and within the past two years had had from seven to 10 upper respiratory infections yearly.

Examination revealed the patient to be well developed and well nourished. The temperature was 99° F. Crepitant râles were audible at both bases posteriorly. Sputa were negative for acid-fast bacilli but contained *Streptococcus viridans*. A chest roentgenogram taken on September 10, 1951, prior to hospitalization (figure 1), showed a circumscribed mass about 5.5 cm. in diameter in the right mid-lung field

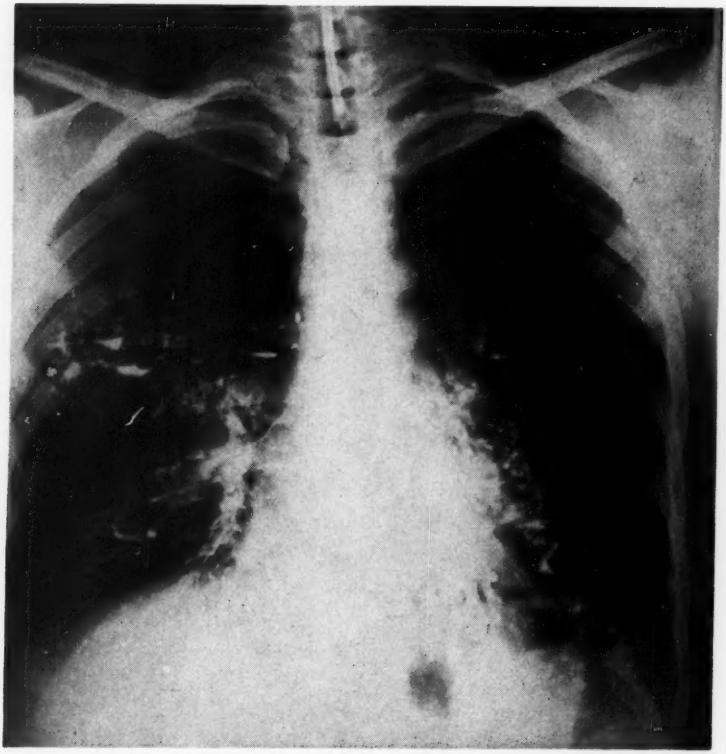

FIG. 2. *Case 1.* Bronchogram on May 20, 1952, reveals saccular and cylindric bronchiectasis bilaterally. There is saccular bronchiectasis at the site of the circumscribed density in the right mid-lung field. The nodular density in the left mid-lung field, previously observed on the ordinary films, is now partially filled with Lipiodol.

and a nodular density approximately 2.5 cm. in diameter in the left mid-lung field. The chest film on admission showed essentially the same features. A bronchoscopic examination on May 16, 1952, showed a thickened and widened carina and a small amount of exudate in both lower lobe bronchi. On May 20 bronchography was performed (figure 2) which clarified the nature of the pulmonary disease. The large density in the right lung filled partially with iodized oil, disclosing underlying

saccular bronchiectasis. There was blockage of the bronchus draining the nodular area in the left lung, probably due to inspissation of the bronchiectatic cavity and its communicating bronchus. In addition, the instilled contrast oil disclosed diffuse saccular and cylindrical bronchiectasis bilaterally. Following treatment with penicillin administered by aerosol inhalation and parenterally, serial roentgenograms displayed progressive resolution of the circumscribed densities in both lung fields. Surgical intervention was not considered advisable because of the presence of extensive bronchiectasis bilaterally.

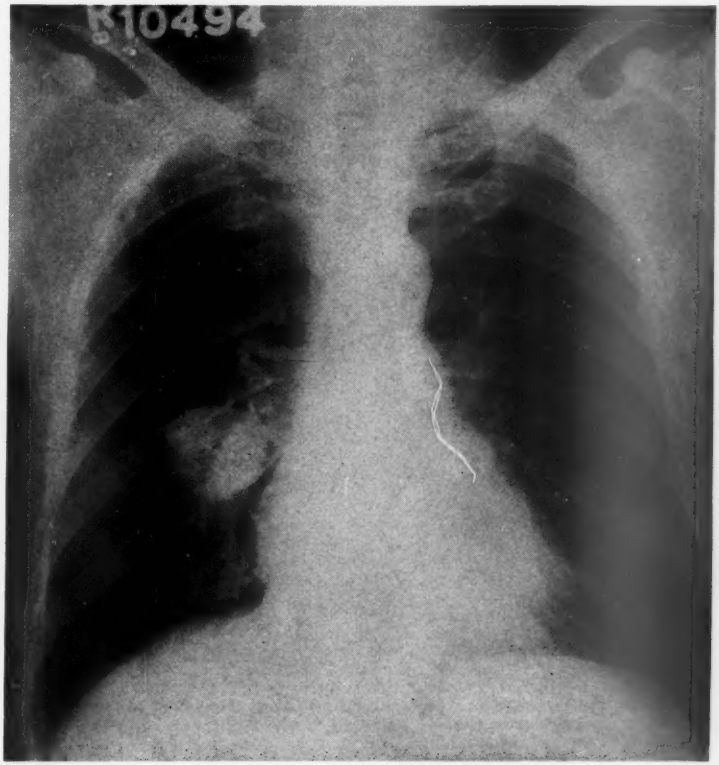

FIG. 3. *Case 2.* Chest roentgenogram taken on March 15, 1954, shows a well defined nodular density about 5 cm. in diameter, located in the right lung field, adjacent to the lower pole of the right hilum.

Comment: The patient was discovered to have nodular pulmonary densities following a routine film taken during the course of employment. At this time he was practically symptom-free, except for a long-standing chronic cough. When changes in the appearance of these shadows were noticeable on serial films the possibility of a primary or metastatic pulmonary neoplasm

was under consideration. Bronchography indicated that bronchiectasis was responsible for the circumscribed densities visible on the ordinary chest roentgenograms.

Case 2. This 56 year old white male was admitted to the Brooklyn Veterans Administration Hospital on March 11, 1954, for evaluation and treatment of a solitary nodular density in the right lung field visualized on a routine employment chest roentgenogram. With the exception of a chronic cough of many years' duration he had no symptoms referable to the respiratory system. The general physical examination revealed no significant abnormalities. The lungs were normal to per-

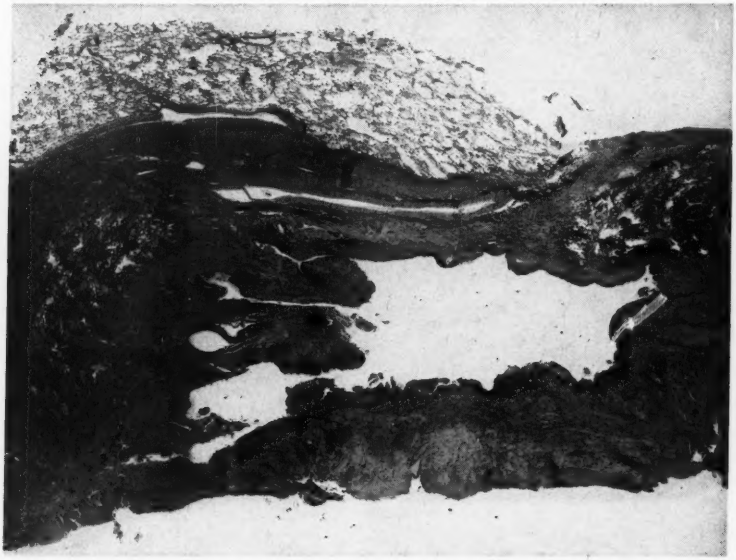

FIG. 4. *Case 2.* Histologic section from representative portion of the lesion (low power photomicrograph) reveals a bronchiectatic cavity lined with metaplastic squamous epithelium. In some areas, necrotic and mucoid material is attached to the cavity wall. The wall of the bronchus is considerably thickened. Dense fibrous tissue and aggregates of lymphocytes are present within its wall. The adjacent pulmonary parenchyma is well aerated and normal in appearance.

cussion. On auscultation scattered rhonchi were heard at both bases. The sputa were persistently negative for acid-fast bacilli on smear and concentration. The predominant organisms in the sputa were *Str. viridans, Neisseria catarrhalis* and hemophilus organisms. The chest roentgenogram taken on March 15 (figure 3) revealed a well demarcated density approximately 5 cm. in diameter in the superior segment of the right lower lobe. Tomographic views demonstrated this density to be sharply circumscribed and to lie in close proximity to the oblique interlobar fissure. Bronchoscopic examination disclosed an essentially normal bronchial tree. Aspirates from the right main bronchus and its lower tributaries were negative for malignant cells by the Papanicolaou technic. A left scalene lymph node biopsy revealed only

hyperplasia of the lymphoid follicles microscopically. The clinical impression was that the density in the right lung field represented a bronchogenic carcinoma.

On March 23 a right thoracotomy was performed. The hilar nodes were enlarged and matted together. Since the pulmonary involvement was considered to be malignant, both the right lower and middle lobes were resected. The postoperative course was uneventful. Gross examination of the resected specimens revealed an inspissated cavity in the superior segment of the right lower lobe approximately 5 cm.

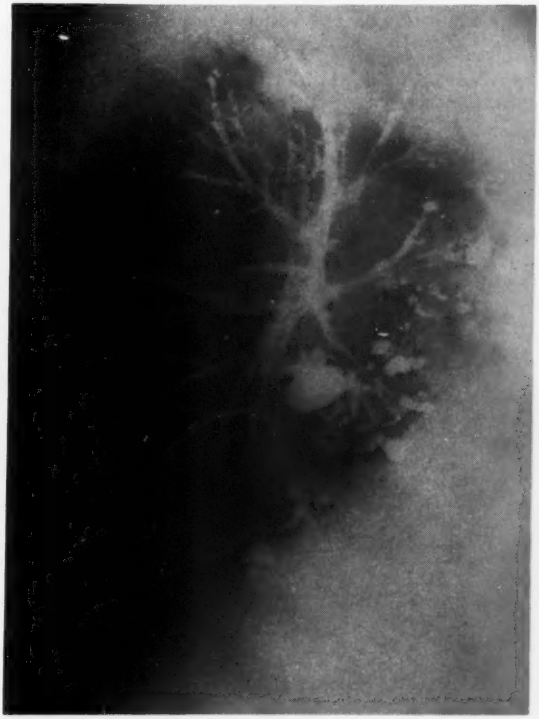

FIG. 5. *Case 3.* Bronchogram, left lateral view, on September 24, 1949, reveals extensive saccular bronchiectasis involving the anterior and lingular divisions of the left upper lobe bronchus, as well as the anterior basal branches of the left lower lobe bronchus. The nodular lesion previously noted in the left lower lung field, behind the cardiac shadow on the ordinary film, is now filled with the contrast substance.

in diameter. The cavity wall varied from 0.3 to 0.5 cm. in thickness. In its major aspects the cavity wall was rigid, firm and cartilaginous in consistency. The cavity lumen was filled with tenacious and homogeneously inspissated mucoid material. The cavity communicated with a segmental bronchus, the lumen of which was considerably narrowed but patent. Microscopically (figure 4) the cavity wall was lined with ciliated and pseudostratified columnar epithelium. Chronic inflammatory cells consisting of fibroblasts, neutrophils, macrophages and aggregates of lymphocytes were scattered through the bronchial wall and adjacent tissues.

Comment: This is a case with localized bronchiectatic dilatations in the superior segment of the right lower lobe which was filled with inspissated mucoid material and presented itself on the usual chest film as a solitary, sharply demarcated mass. The roentgen features of the lesion closely simulated a bronchogenic neoplasm. Bronchography was not performed and might have aided in elucidating the nature of this circumscribed density. The true pathologic condition was demonstrated only by histologic examination of the involved portion of lung which was resected.

Case 3. This 47 year old white male was hospitalized for evaluation of a nodular lesion in the left lower lung field, which was discovered on a routine roentgen survey. The history elicited few symptoms of significance, except for a slight chronic cough

FIG. 6. Histologic section through the nodular lesion (low power photomicrograph) shows a bronchiectatic sac lined by columnar epithelium. Necrotic and mucoid material is attached to its inner wall. Considerable fibrous tissue and aggregates of inflammatory cells are present within its wall.

which the patient attributed to excessive cigarette smoking. Approximately five years prior to admission he had experienced a small hemoptysis of bright red blood. However, he was not hospitalized, nor was a chest roentgenogram taken at that time. Physical examination revealed scattered fine râles at the left lower lung posteriorly. Sputa were negative for acid-fast bacilli, but showed a mixed flora of organisms on culture. Bronchoscopic examination revealed the tracheobronchial tree to be essentially normal. A small amount of thick mucoid material was present in the bronchial branch of the left lower lobe. This bronchial exudate was examined for tubercle bacilli and malignant cells, with negative results. A chest roentgenogram taken on September 18, 1949, disclosed a round density approximately 2 cm. in diameter, behind the cardiac shadow. It was the clinical impression that this nodule was a benign tumor, in the nature of a hamartoma, tuberculoma or bronchial adenoma. A bron-

chography performed on September 24 (figure 5) demonstrated that the nodular shadow filled with iodized oil and that it communicated directly with a segmental bronchus of the left lower lobe. There was associated saccular bronchiectasis involving the lingular bronchial branches of the left upper lobe, as well as the anterior basal bronchi of the left lower lobe.

On October 10 a resection of the lingula of the left upper lobe and the basal segments of the left lower lobe was performed. The postoperative course was uneventful. Histologic examination of the resected specimen (figure 6) showed the nodule to be an inspissated bronchiectatic sac. The wall was lined by columnar epithelium, with necrotic and mucoid material attached to the major portion of its

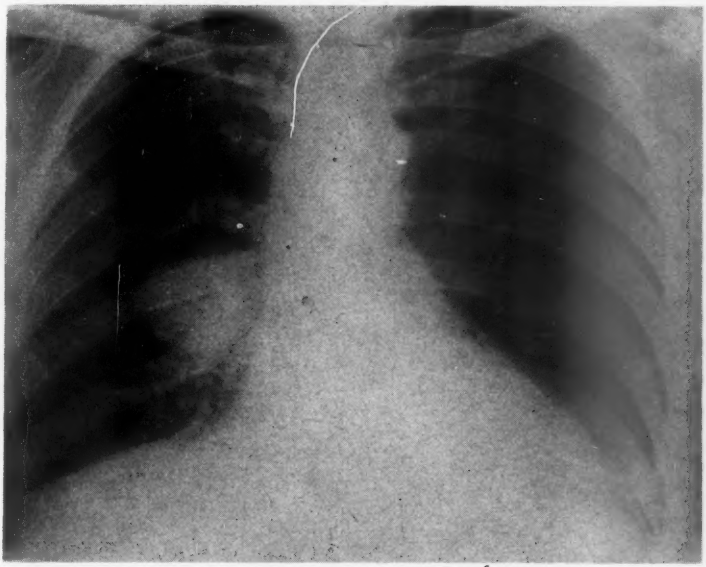

FIG. 7. *Case 4.* Chest roentgenogram taken on July 7, 1950, shows a circumscribed density about 5 cm. in diameter adjacent to the right hilum. A suggestive fluid level is present at the upper margin of this density.

lining. Extensive chronic inflammatory changes were also present within the wall of the bronchus.

Comment: This case is one with an essentially silent nodular lesion in the left lung, first recognized on a routine chest roentgenogram and suspected of being a benign tumor. Preoperative bronchographic studies demonstrated that this density consisted of a partially inspissated bronchiectatic cavity. The diagnosis was confirmed by histologic examination following resection of the affected lung segments.

Case 4. This patient was a 36 year old white male admitted to the Brooklyn Veterans Administration Hospital on July 7, 1950, because of intermittent paroxysms

of coughing and blood streaking of sputum of one week's duration. On the day prior to admission the patient had experienced a hemoptysis of about 200 c.c. of bright red blood. On physical examination fine râles were heard at both lung bases. The chest roentgenogram taken on July 7 (figure 7) displayed a round density approximately 5 cm. in diameter in the right mid-lung field adjacent to the mediastinum. A suggestive fluid level was present at the superior margin of this mass. The surrounding pulmonary parenchyma was clear. The bronchovascular markings at the right base were prominent, and platelike atelectasis was present at the right base. The clinical impression on admission was that the pulmonary mass consisted of a tumor which had undergone secondary necrosis. Bronchoscopic examination performed on July

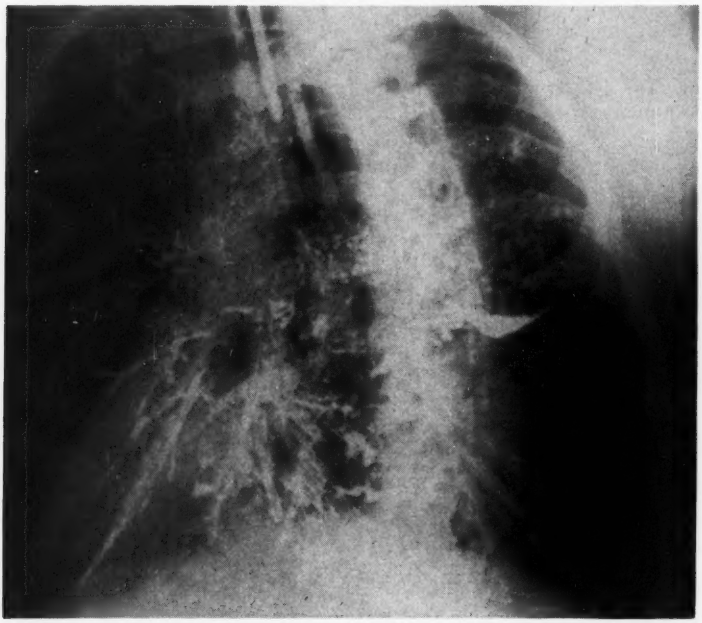

FIG. 8. *Case 4.* Bronchogram, right anterior oblique view, on August 3, 1950, demonstrates that the density, which is located in the superior segment of the right lower lobe, is partially filled with the contrast medium.

12 disclosed a thickened, edematous carina and bloody exudate emanating from the right lower lobe bronchus. Bronchography on August 3 (figure 8) showed cylindrical dilatations of the basal segmental bronchi of both lower lobes. The cystic structure in the superior segment of the right lower lobe filled with iodized oil.

On September 27 excision of the superior segment of the right lower lobe was performed. The postoperative course was uneventful. Examination of the resected specimen showed that the parenchyma of the involved segment was replaced by a large bronchiectatic cavity. The inner wall of this cavity was lined by a smooth, glistening surface. The lumen of the cyst communicated with a markedly narrowed but patent segmental bronchus. Histologic examination of the tissue demonstrated

that the cavity wall was composed of columnar and pseudostratified columnar epithelium. The wall contained all elements of bronchial structure (figure 9).

Comment: This patient developed sudden bouts of pulmonary hemorrhage necessitating emergency hospitalization. On radiologic examination a rounded mass about 5 cm. in diameter with a fluid level at its superior margin was discovered in the right lung field. This mass was believed to represent a tumor which had undergone necrosis. Following resection of the superior segment of the right lower lobe, histologic examination disclosed that the pulmonary mass was a large, inspissated bronchiectatic cavity.

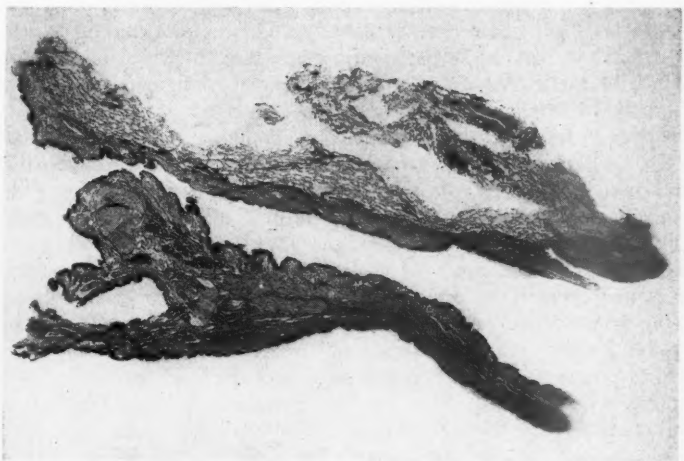

FIG. 9. *Case 4.* Histologic section through the circumscribed lesion (low power photomicrograph) reveals a bronchiectatic dilatation lined by columnar and pseudostratified columnar epithelium. All bronchial tissue elements are present. The adjacent lung parenchyma is atelectatic.

PATHOGENESIS AND PATHOLOGY OF LOCALIZED BRONCHIECTASIS

A conglomeration of localized, saccular bronchiectatic dilatations may produce one irregular cavity which grossly may resemble a chronic lung abscess. Microscopically, we find that when the inflammatory process is still active the destroyed portions of the bronchial walls may be largely replaced by granulation tissue. In those chronic cases where the inflammation has been stabilized or overcome, the purulent exudate lining the cavity walls may have been removed and the destroyed epithelial lining may now be replaced by an irregular layer of epithelial cells. These have a tendency to metaplasia, chiefly in the form of a variety of cuboidal or squamous cells. In chronic, burnt out cases of localized bronchiectasis, it may be impossible to determine the etiology of the bronchial dilatations, since all gross or even

microscopic evidence of inflammation may no longer be apparent. These cystic bronchial dilatations may then be regarded as congenital in origin, resulting from defective embryonic development of a portion of the bronchial tree. We can see, however, that infection with destruction of the epithelium and a variable portion of the bronchial wall may have occurred early in childhood or in infancy following one of the exanthemata or associated with an episode of "influenza" or "virus pneumonia." The development of destructive bronchial disease may not have been appreciated clinically at that time. Years later, when all signs of inflammation have subsided and the destroyed mucosa has been reëpithelialized, it may be impossible to state from clinical study, roentgenography or even on histologic examination of the tissues whether these cystlike cavities, commonly referred to as bronchial cysts or bronchogenic cysts, were preceded by suppurative infection of the bronchial walls or whether they originated directly from embryonic maldevelopment of the bronchi.

However, it is probable that infection is not the sole factor responsible for the development of localized bronchiectasis. Predilection for the appearance of bronchiectasis in one portion of the bronchial tree may also be dependent on a variety of mechanical factors, both those of developmental origin (concerning which we do not as yet have precise knowledge), and those resulting from acquired pathologic conditions. These mechanical factors may impair the drainage from a particular bronchial segment by causing variable degrees of bronchial obstruction. This may well be responsible for the eventual occurrence of chronic suppurative infection, with irreparable changes in the particular portion of the bronchial tree. At other times, as a consequence of the constant operation of bronchial check valve obstruction due to the existence of minor developmental abnormalities, gradual and progressive dilatation of the bronchi distal to the obstruction will occur even without the superimposition of infection and associated bronchial wall damage. In such instances the dilated bronchi may be truly considered as of congenital origin. If the bronchial dilatation is great, a bronchial cyst will form which may be filled with fluid, air, or both, depending upon whether free communication with the bronchus at its origin is maintained. Bronchography will often be of no aid in establishing the diagnosis, since the communication of the cyst stalk with the bronchus at its origin may become either completely obliterated or narrowed to such a degree that entrance of the contrast material into the cyst is prevented.

Shaw [9] described the entity of "mucoid impaction of bronchi," which is characterized by a localized accumulation of inspissated mucus in the second order branch bronchi, in cases with asthma and chronic obstructive bronchitis. The inspissated mucus is tenacious, putty-like in consistency, and greenish gray in appearance. The roentgen density is due either to segmental atelectasis, chronic pneumonitis, abscess formation or an inspissated bronchial dilatation. Ramsay and Byron [10] reported several cases of con-

genital bronchogenic cysts in which a thin septum produced a check valve type of atresia of the bronchial lumen, with resultant dilatation of the bronchial walls distal to the obstruction.

Undoubtedly other congenital or acquired mechanisms may similarly be responsible for development of localized bronchial dilatations, either through operation of a check valve mechanism alone or by favoring persistence of chronic suppuration, with resultant irreversible damage to the integrity of the bronchial walls.[11-14] Therefore, the clinical differentiation between congenital bronchogenic cysts and acquired bronchiectasis, although well defined in most cases, may become tenuous when the bronchiectasis is well circumscribed and all signs of infection have abated. The distinction may then be impossible even on histologic examination of tissue sections. Absence of inflammatory reaction and presence of a uniform epithelial lining composed of flattened columnar or cuboidal epithelial cells may suggest a congenital origin. The presence of chronic inflammation in the bronchial walls and in the surrounding tissues of the lung, as well as epithelial metaplasia of the dilated bronchial lumina, may point to an acquired etiology. However, it is well recognized that these are not by any means true indications of the congenital or acquired origin of bronchial dilatations, since all signs of infection may have disappeared from the walls of acquired, chronic bronchiectatic sacs, whereas infection may have been superimposed on congenital bronchiectatic cysts.

Clinical Features and Differential Diagnosis of Localized Bronchiectasis

Frequently the area of localized bronchiectasis may not cast a shadow or cause significant displacement of the pulmonary contents on the chest roentgenogram. The patient may also manifest no striking respiratory symptoms. The bronchiectasis may then remain unrecognized and continue to be clinically dormant for a long time. The existence of some form of underlying pulmonary disease may be suggested in time, following repeated exacerbation of upper respiratory infections. A definitive diagnosis can be established only if bronchographic studies are performed. When a bronchiectatic cavity becomes inspissated with exudate and surrounded by an area of interstitial pneumonitis it may be apparent radiologically as a circumscribed area of increased density. Where the patient manifests symptoms and signs of a febrile illness, this pulmonary involvement may be attributed to a chronic lung abscess or to a localized area of bacterial or viral pneumonia. Occasionally, when the mass is localized to an upper lobe, it may simulate pulmonary tuberculosis roentgenologically. Treatment with antibiotics may cause a favorable clinical response, with resolution of the roentgen shadow. The underlying bronchiectasis, however, will continue to remain unrecognized and undiagnosed unless this clinical syndrome is appreciated and a confirmatory bronchographic examination is accomplished.

These pulmonary nodules are often detected initially in apparently well persons following routine roentgen examinations of the chest. In such cases the circumscribed pulmonary lesions may have to be differentiated from tuberculomas, localized fungus infections of the lungs such as histoplasmosis and coccidioidomycosis, or from pulmonary neoplasms. Usually the thought uppermost in the clinician's mind is the possibility that the nodular density may represent a tumor of the lung of either benign or malignant variety. When thorough investigations fail to give a precise indication of its pathologic nature, the chief fear is that the lesion may represent a silent peripheral carcinoma of the lung. For this reason an exploratory thoracotomy is then considered mandatory.[15-18] The correct diagnosis may be established only later, when the specimens are examined histologically.

The value of bronchography in the preoperative diagnosis of all isolated pulmonary lesions is therefore stressed. Bronchographic mapping should be complete. At times it may disclose that the bronchiectasis is confined entirely to one segment or subsegment, and that it is responsible for the circumscribed shadow on the roentgenogram. These cases are ideally suited for resection. In other instances bronchography will disclose, in addition, extensive cylindric or saccular bronchiectasis involving both lungs, in the absence of roentgen or clinical indication of such diffuse disease. In these cases surgical procedures are of doubtful value.

Summary

1. Bronchiectasis may be a localized disease involving only a portion of a single lung segment or subsegment.

2. Localized bronchiectatic dilatations often fail to cast shadows on routine chest films.

3. At other times the localized bronchial dilatations become filled with fluid and surrounded by zones of pneumonitis, producing circumscribed, rounded shadows on the usual chest films.

4. These nodular densities may simulate tumors of the lung.

5. The studies carried out for the evaluation of circumscribed pulmonary densities frequently do not include bronchography.

6. Bronchography can reveal graphically that pulmonary "coin" lesions noted on ordinary chest roentgenograms may be manifestations of localized bronchiectasis.

7. This simple procedure may clarify the diagnosis and indicate the treatment required.

8. Many unnecessary exploratory thoracotomies may thereby be obviated.

Summario in Interlingua

Bronchiectasis pote prender le forma de un morbo localisate afficiente un sol segmento o subsegmento pulmonar. Le differentiation inter acquirite bronchiectasis e congenite cystos bronchogene es satis simple in le majoritate del casos, sed illo pote

devenir difficile quando le ectasis bronchial es nettemente circumscribite e quando omne signos del infection ha disparite. In tal casos le differentiation pote devenir impossibile, mesmo per medio de examines histologic de sectiones de texito.

Un area de bronchiectasis localisate non produce necessarimente un umbra roentgenologic. Alora le existentia del primari morbo pulmonar pote suspicer se in le curso del tempore si il occurre repetite infectiones exacerbate del vias respiratori, sed un definitive diagnose non pote esser establite usque un examine bronchographic es executate.

Quando le saccos bronchial es plenate de fluido e cincturate de zonas de pneumonitis, illos es visibile in le usual roentgenogramma thoracic como localisate umbras rotunde. In ille patientes qui manifesta symptomas e signos de un morbo febril, iste affection pulmonar pote esser attribuite a un abscesso pulmonar o a un localisate area de pneumonia bacterial o virusal. Quando le massa se trova in un lobo superior, su representation roentgenologic pote simular etiam tuberculosis pulmonar.

In altere casos, nonobstante, iste nodulos pulmonar es detegite in roentgenogrammas routinari del thorace de personas apparentemente in bon stato de sanitate. In tal casos le circumscribite lesiones pulmonar debe esser differentiate ab tuberculomas, ab localisate infectiones fungal del pulmones (como per exemplo histoplasmosis e coccidioidomycosis), e ab neoplasmas pulmonar.

Un revista del litteratura indica que le technicas diagnostic usate in evalutar circumscribite densitates pulmonar include frequentemente nulle studio bronchographic. Pro iste ration nos sublinea le valor del bronchographia in le diagnose preoperative de omne isolate lesiones pulmonar. Non infrequentemente le bronchographia pote demonstrar graphicamente que certe rotunde lesiones pulmonar visibile in le routinari roentgenogramma thoracic es manifestationes de localisate bronchiectasis. Alora le simple technica bronchographic pote clarificar le diagnose e indicar le tractamento a usar. Assi le bronchographia pote adjutar nos a evitar multe innecessari thoracotomias exploratori.

Nos ha observate un serie de 6 bronchiectases localisate que simulava neoplasmas pulmonar. In le presente studio nos reporta 4 casos illustrative.

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PARTIAL EVENTRATION OF THE RIGHT DIAPHRAGM (CONGENITAL DIAPHRAGMATIC HERNIATION OF THE LIVER) *

By ALFRED VOGL, M.D., F.A.C.P., *New York, N. Y.*, and ALLAN SMALL, M.D., *Bridgeport, Connecticut*

TOTAL eventration of one hemidiaphragm (relaxatio diaphragmatica), more often seen on the left side, is a well known congenital anomaly.[4, 19, 34] The occurrence of a *partial* eventration of the diaphragm, however, has attracted less attention, at least in the American literature.[5, 15, 20, 33] This condition, nevertheless is of interest in several respects: (a) It is not at all a rarity. (b) It is remarkable for its virtually exclusive occurrence on the right side and its predilection for the antero-median portion of this hemidiaphragm. (c) Its radiologic picture is sufficiently characteristic to allow the correct diagnosis to be made with reasonable certainty from the appearance alone. Conversely, it may present a puzzling problem to those unfamiliar with the entity and has often led to unnecessary anxiety and even needless surgical exploration.[19, 26, 41]

Six cases illustrating this condition have been collected in a period of less than one year. Their records will be briefly reported, with emphasis upon the radiologic findings which, as will be seen presently, show a striking similarity.

CASE REPORTS

Case 1. A 62 year old white man was admitted because of a chronic duodenal ulcer with recurrent gastric dilatation. On fluoroscopy, the right diaphragm was found to bulge upward in its medial and anterior portion (figure 1). The highest point of the protruding shadow extended to three fingerbreadths above the left diaphragm. The outlines of the bulge were smooth and rose rather steeply medially and anteriorly, beginning from a point about two fingerbreadths above the level of the left diaphragm, while laterally, and particularly posteriorly, they sloped more gradually down into the peripheral portions of the diaphragm. The shadow showed paradoxic motion on respiration. Following a diagnostic pneumoperitoneum the liver shadow was seen to separate from the diaphragm (figure 2). The latter was now visible as a thick, slightly curved line except in its antero-median portion, which stood out as a fine, semicircular arch, projecting upwards like the silhouette of a large air bubble. Correspondingly, a rounded hump could be seen superimposed upon the superior surface of the right lobe of the liver.

Partial gastrectomy was performed for the peptic ulcer. At this occasion the antero-median portion of the right diaphragm was found markedly thinned and bulging into the thorax.

Case 2. A 62 year old white woman was admitted for inoperable ovarian carcinoma with widespread metastases.

* Received for publication December 23, 1954.
From the Division of Medicine, Metropolitan Hospital, New York, N. Y.

FIG. 1. *Case 1.* A 62 year old man, admitted for peptic ulcer, showing a convex, rounded shadow rising from the antero-medial portion of the right diaphragm. The convex segment moved paradoxically on inspiration.

FIG. 1. *Case 1.* A 62 year old man, admitted for peptic ulcer, showing a convex, rounded shadow rising from the antero-medial portion of the right diaphragm. The convex segment moved paradoxically on inspiration.

FIG. 2. *Case 1.* Diagnostic pneumoperitoneum separates a smooth semi-circular mass on top of the right lobe of the liver from a thin line representing a pouch of the diaphragm.

FIG. 3. *Case 2.* A 62 year old woman, with ovarian carcinoma and metastases to the liver. Postero-anterior view shows a round, orange-size shadow filling the right cardiophrenic angle. Right anterior and oblique views show the mass to be situated anteriorly, inseparable from the liver shadow and the lower anterior chest wall.

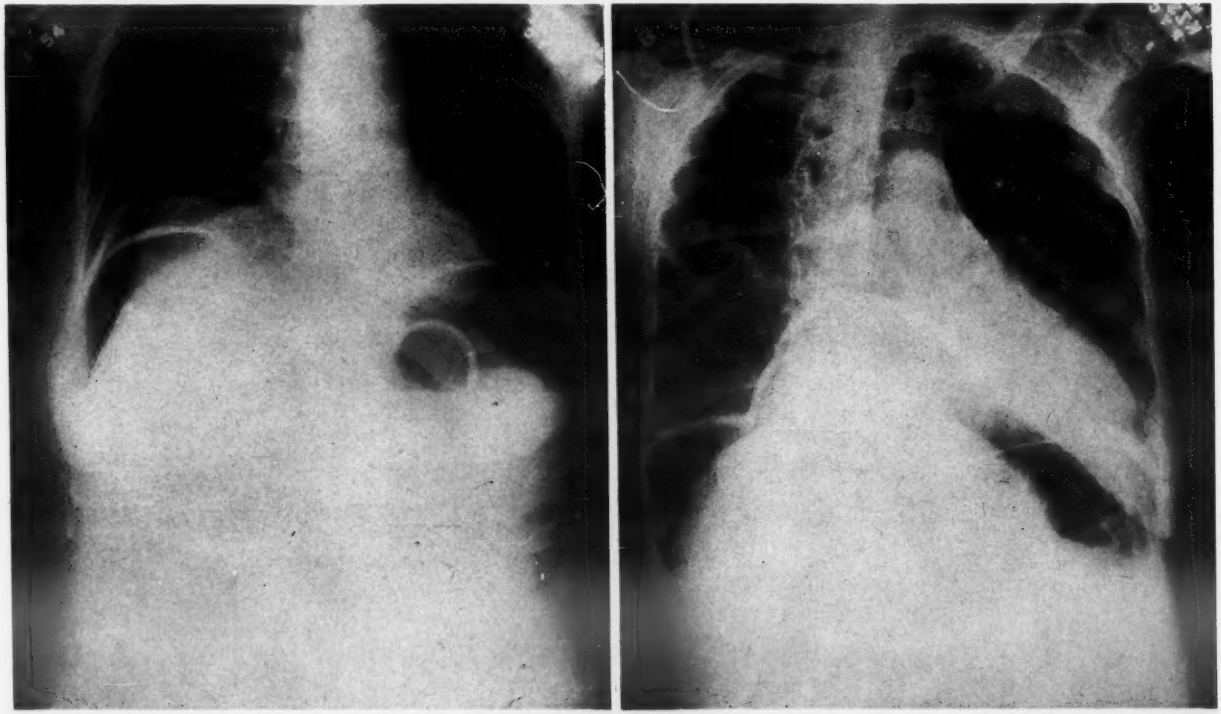

FIG. 4. *Case 2.* Pneumoperitoneum separates the entire liver from the diaphragm. It shows the normal portion of the diaphragm and the large pouch in postero-anterior and right oblique views. The hump on top of the convexity of the liver is clearly seen in both views.

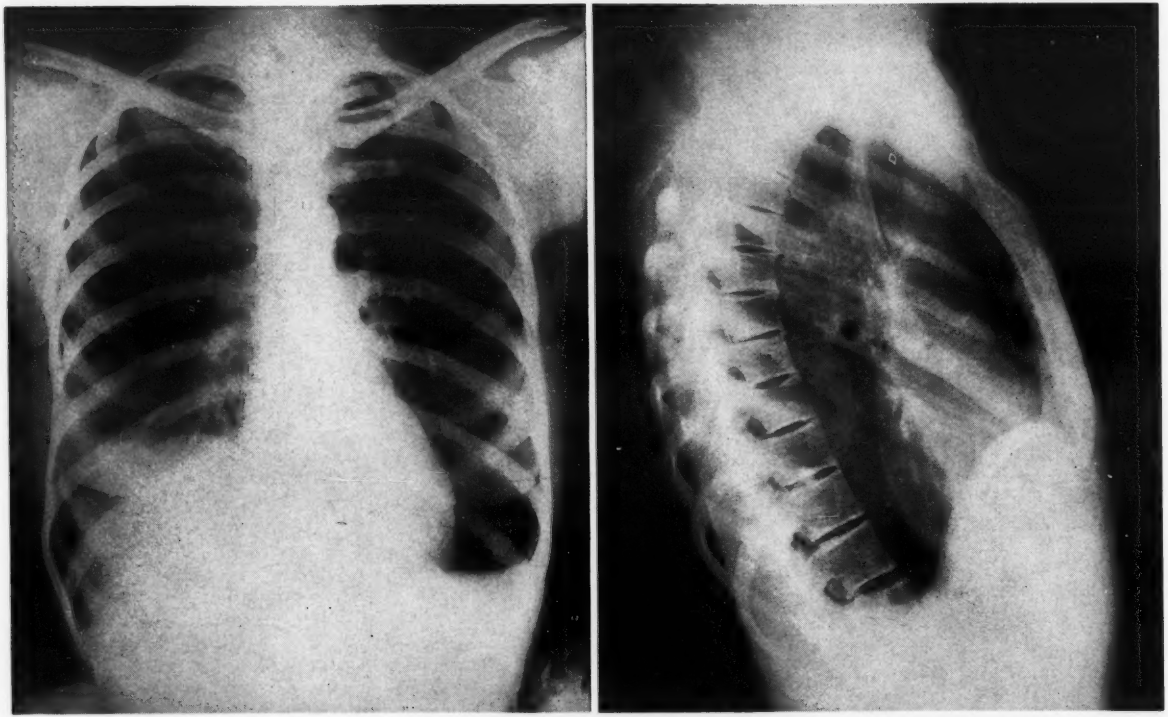

FIG. 5. *Case 3.* A 49 year old woman, routine examination. Chest films show large ovoid shadow filling the right costophrenic angle on postero-anterior view and lying close to the anterior chest wall on right lateral view. Pneumoperitoneum demonstrated a well circumscribed accessory lobe of the liver on top of the right lobe.

A roentgenogram of the chest revealed an orange-size homogeneous shadow at the base of the right lung, filling the cardiophrenic angle and the anterior costophrenic sinus in the postero-anterior and right lateral views, respectively (figure 3). Diagnostic pneumoperitoneum showed the right diaphragm as a thick curved line in sagittal view (figure 4). In addition, another curve became visible, and this projected semicircularly from the line of the diaphragm to a level two to four fingerbreadths higher. This pouch was more clearly visualized in the right anterior oblique view, abruptly jutting out of the ventral portion of the hemidiaphragm. On top of the liver a large rounded hump surmounting its convex surface became visible.

At autopsy the liver capsule was found to be studded with metastases. These had invaded the parenchyma, including an accessory lobe which projected from the superior surface of the right lobe and completely occupied a diaphragmatic pouch. The wall of this sac was very thin, white and glistening.

Case 3. A routine x-ray of the chest taken on a 49 year old white woman revealed a sharply outlined, dense, hemispheric shadow, inseparable from the diaphragm, in the right cardiophrenic angle (figure 5). A right lateral view localized this mass close to the anterior chest wall, its outline sloping gradually towards the center of the right diaphragm. Diagnostic pneumoperitoneum showed an orange-size, smooth, rounded mass attached to the superior border of the liver and separated from a thin-walled, semicircular diaphragmatic pouch.

Case 4. A 78 year old white male was admitted because of an ulcerated carcinoma of the oral mucosa with metastases to the regional lymph nodes, the lungs and the liver. The latter was large, hard and grossly irregular.

In addition to metastatic pulmonary lesions, x-ray of the chest revealed a large, semicircular, somewhat scalloped shadow protruding from the contour of the antero-median half of the right diaphragm into the lung field (figure 6). On lateral view the shadow appeared to rise above the diaphragmatic dome in a mushroom-like fashion. The diaphragm could not be completely separated from the hepatic protuberance by intraperitoneal air insufflation (figure 7), indicating either invasion of the metastatic carcinoma from the liver into the diaphragm or, more probably, involvement of the "bare area" of the liver surface [41] in the herniation. Autopsy was not performed.

Case 5. A 63 year old white woman was examined because of increasing constipation.

A roentgenogram of the chest showed a rounded, sharply outlined, orange-size homogeneous shadow arising from the right diaphragmatic contour. Medially it was inseparable from the cardiac border, but anteriorly (in right lateral view) about 1.5 cm. of translucent lung parenchyma was visible between the chest wall and the mass (figure 8). In this location a small segment of normal diaphragm could be seen from which the ventral contour of the mass rose like a mushroom. The mass had first been noted five years earlier and had since remained unchanged. For this reason no further diagnostic measures were considered indicated.

The sixth case of our series differs from the others in regard to the localization of the diaphragmatic pouch.

Case 6. A 72 year old man was admitted because of generalized atherosclerosis and malnutrition.

In addition to extreme tortuosity of the thoracic aorta which deviated to the right, x-ray examination of the chest revealed a rounded mass at the right base. It arose from the central portion of the diaphragm (on postero-anterior, right oblique and lateral views) (figure 9). The outline was smooth, the highest point two to three fingerbreadths above the rest of the diaphragm. The shadow showed paradoxic respiratory motion and reached the size of a grapefruit on deep inspiration. A diag-

angle on postero-anterior view and lying close to the anterior chest wall on right lateral view. Pneumoperitoneum demonstrated a well circumscribed accessory lobe of the liver on top of the right lobe.

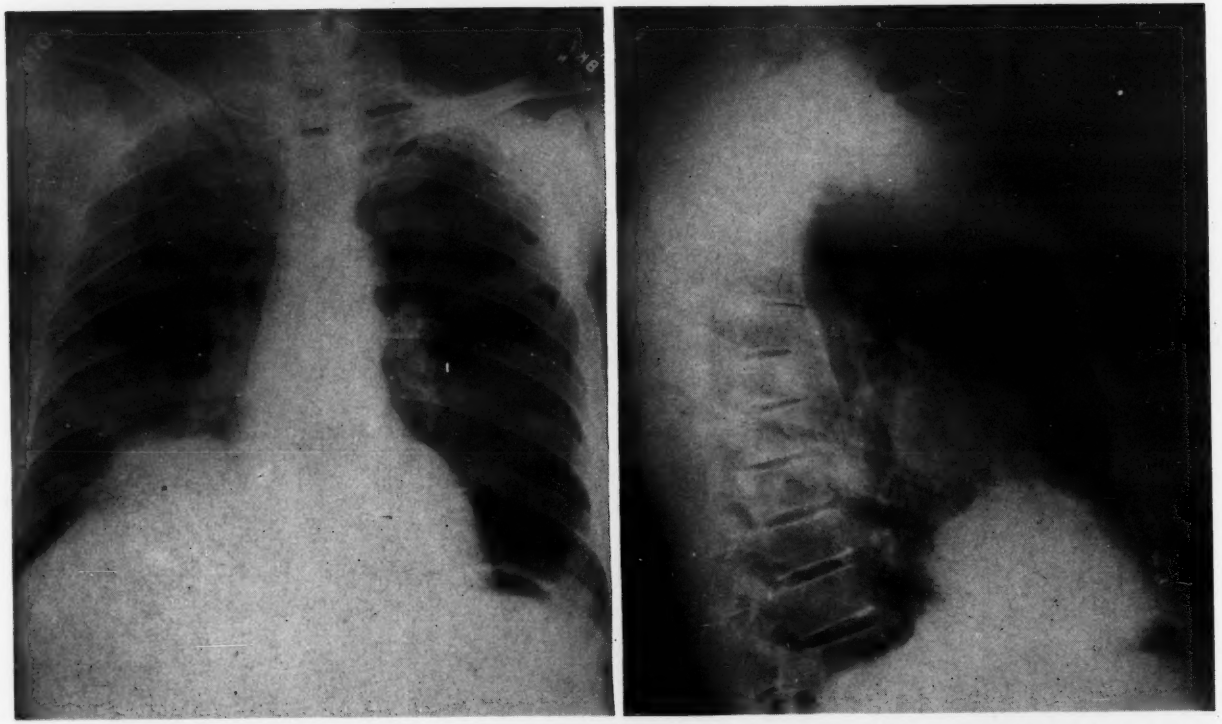

FIG. 6. *Case 4.* A 78 year old man with cancer of the mouth and metastases to the lungs and liver. Postero-anterior and right lateral views show a very large, scalloped, slightly mushroomed mass rising from the antero-median portion of the diaphragm.

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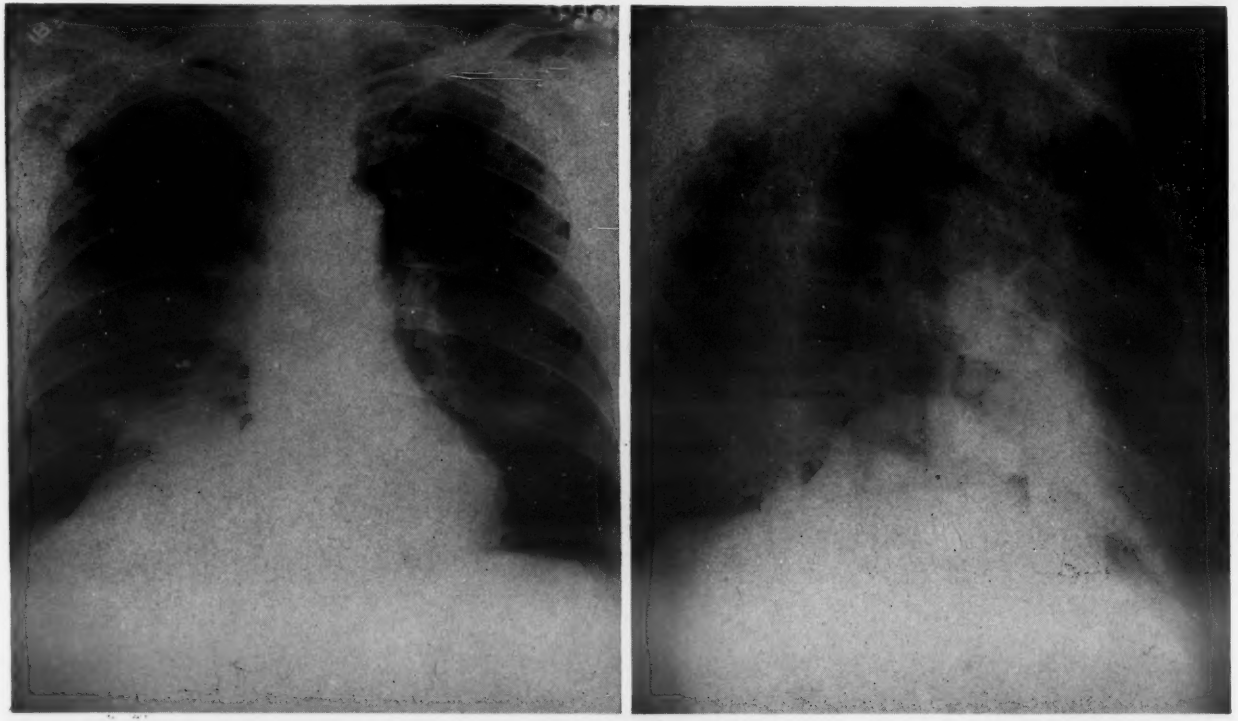

FIG. 7. *Case 4.* Pneumoperitoneum shows a very small accumulation of air between the hump of the liver and the thin wall of the diaphragmatic pouch.

FIG. 8. *Case 5.* A 63 year old woman, examined because of increasing constipation. A mushroom-like, orange-size shadow is seen confluent with the antero-median shadow of the diaphragm, but separated from the anterior chest wall by normal lung parenchyma. The mass had been known to exist for at least five years and did not give rise to any symptoms.

confluent with the antero-median shadow of the diaphragm, but separated from the anterior chest wall by normal lung parenchyma. The mass had been known to exist for at least five years and did not give rise to any symptoms.

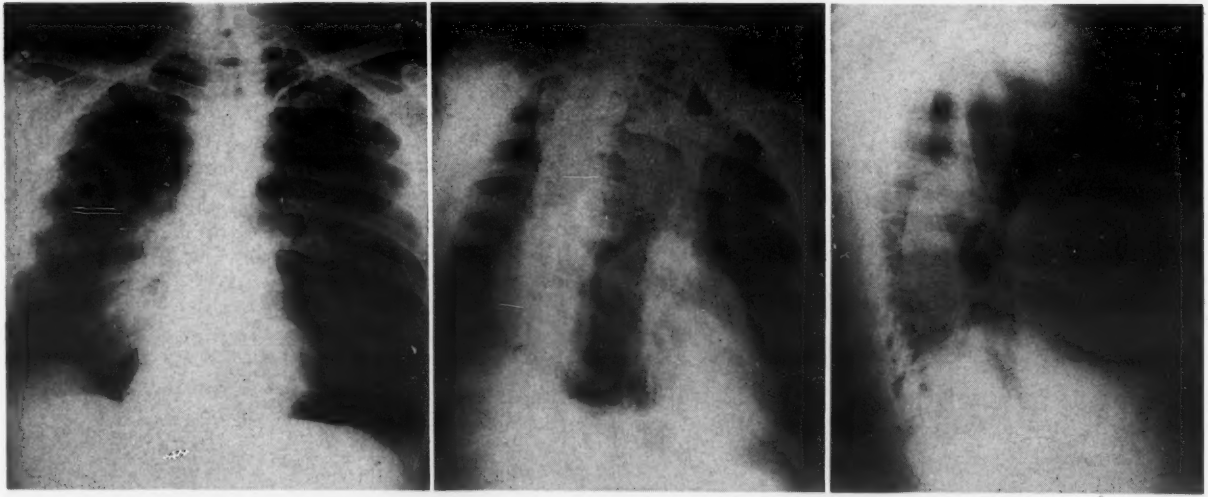

FIG. 9. *Case 6.* A 72 year old man, with generalized atherosclerosis. Chest film shows a grapefruit-size shadow superimposed upon, and inseparable from, the right diaphragm. It is situated over its central and postero-lateral portion and reveals paradoxical movement on inspiration. The aorta is dilated and curving to the right.

FIG. 10. *Case 7.* Pneumoperitoneum separates a smooth, rounded hump on the center of the convexity of the liver (on lateral view) from a thin-walled large pouch of the dome of the right diaphragm.

nostic pneumoperitoneum revealed a thin-walled, sharply circumscribed upward bulge of the dome of the right diaphragm, and a smooth-walled, rounded prominence of the liver, protruding into the diaphragmatic pouch from the center of the superior surface of the right lobe (figure 10).

Discussion

The cases described above illustrate the characteristic features of a condition commonly referred to as *partial eventration of the right diaphragm.* The corresponding deformity of the liver has for generations been familiar to the pathologists as a *superior accessory lobe* [27] (figure 11), but the radiologic picture was apparently first described by Assmann in 1922.[2] He regarded it as a variation of the common physiologic division of the right diaphragm into two arches.[2, 16] The nature of the condition was first recog-

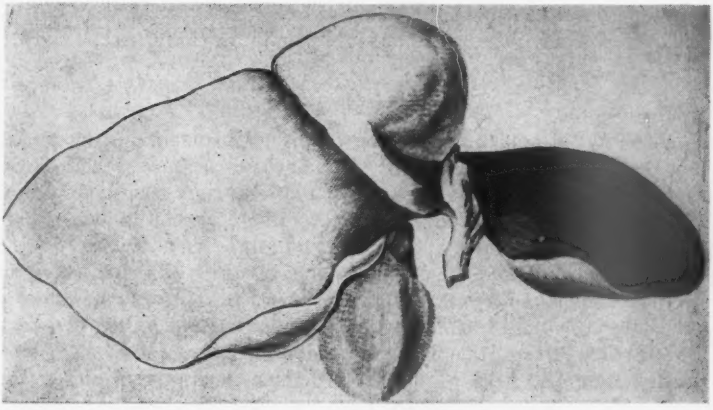

Fig. 11. Liver with a "superior accessory lobe." (From I. F. Meckel: Tabulae anatomico-pathologicae, Leipzig, 1822.[28])

nized and fully described as *"hernia diaphragmatica dextra hepatica"* by Reich (1923),[35] who also used intraperitoneal air insufflation in the x-ray diagnosis of this condition, a procedure introduced by Rautenberg (1914)[32] and recommended for the differentiation of diaphragmatic eventration from herniation by Schlecht and Wels (1919).[39]

Our observations tend to corroborate the impression of earlier authors [5, 35, 41] that, as a rule, partial eventration of the right diaphragm is an incidental finding, entirely innocuous and not the cause of symptoms. It is therefore almost invariably detected during a routine examination or in the course of investigations of symptoms caused by some other disease.

It is by no means a rare condition.[5, 16, 21, 35] From among 857 instances of diaphragmatic hernia, in 14 cases liver alone was found in the hernial sac.[21] It has been found in infants and children [1, 3, 5, 7, 13, 15, 17, 22] as well as in

Fig. 10. *Case 7.* Pneumoperitoneum separates a smooth, rounded hump on the center of the convexity of the liver (on lateral view) from a thin-walled large pouch of the dome of the right diaphragm.

adults. It has proved to be a fertile source of diagnostic errors, since it can be confused either with a variety of tumors or cysts, intrathoracic (pulmonary, pleural, pericardial or mediastinal), diaphragmatic or subphrenic (especially hepatic), or with loculated pleural or pericardial effusions.

To our knowledge, only three cases are on record in which the herniated portion of the liver became strangulated and gave rise to symptoms of intermittent incarceration. One was a 47 year old woman [42] who for six months had experienced attacks of squeezing epigastric pain accompanied by vomiting, lasting three to eight hours. Another was a 44 year old man [8] who for 12 years had suffered episodes of knifelike epigastric pain of a few minutes' duration which were relieved by belching and which gradually gave way to a dull and more constant epigastric aching. In both of these cases a tight band of diaphragmatic tissue was found around the pedicle, and surgical repair produced permanent cure. A third case,[18 (case 2)] a 13 year old boy, complained of occasional episodes of slight pain in the right chest.

Diagnosis

Recognition of partial eventration of the right diaphragm by physical examination is virtually impossible.[20] Dullness to percussion and diminution of breath sounds at the right base anteriorly may conceivably arouse suspicion as to the presence of such a condition, but the ultimate clinical diagnosis must depend upon fluoroscopic and radiographic study.

In the more common type of partial eventration which involves the antero-median part of the right diaphragm (our cases 1 to 5), the radiologic findings are essentially the following: On fluoroscopy a semicircular or semioval, homogeneous, nonpulsating shadow of soft tissue density is seen in the right lung field, arising from the median portion of the diaphragm with a broad base or pedicle. It is situated close to the right cardiac border and fills the cardiophrenic angle. It becomes more prominent on deep inspiration when the lateral and dorsal portions of the diaphragm move downward, while the convex segment either remains at the same level or perhaps even moves upward (paradoxic motion [2, 16, 34, 41, 42]). The mass is usually orange- to grapefruit-size, and its lateral border is more or less sloping and dips into the diaphragm at an angle. In the right lateral view the mass appears close to or inseparable from the anterior chest wall. From here the contour curves slightly upward and continues in a gentle slope posteriorly, merging either gradually or abruptly (at an acute or blunt angle) into the posterior portion of the diaphragm. Radiographic studies demonstrate the location of the mass, its homogeneous nature, the sharp, convex, occasionally slightly scalloped outlines and its continuity with the liver shadow.

In the less common form of partial eventration in which the central portion of the right diaphragm is involved (our case 6), the radiologic findings are the same except for the location of the mass atop the dome of the hemidiaphragm. On postero-anterior view the shadow is found to be

situated more laterally than in the other type, and on right lateral view it is seen behind the cardiac silhouette, somewhat overlapping the dorsal spine. The affected segment of the diaphragm reveals diminished or paradoxic motion with inspiration.

A combination of findings as enumerated is virtually diagnostic of partial eventration of the right diaphragm with herniation of liver into the diaphragmatic pouch. If unequivocal confirmation of this diagnosis is desired it may be obtained by means of an artificial pneumoperitoneum.[10, 12, 31, 35, 39] Intraperitoneal insufflation of 250 to 1,000 c.c. of air by the technics employed in the treatment of pulmonary tuberculosis[28] produces separation of the diaphragm and the liver by a translucent zone of gas. The diaphragm stands out as a thick, occasionally multiple curved line, with a clearly defined, thinner, semicircular pouch projecting upward from its right antero-median or central portion. The silhouette of the convex surface of the right lobe of the liver reveals a conspicuous protuberance which is domeshaped, homogeneous, sharply circumscribed and smoothly outlined. This picture is striking and establishes the diagnosis. Artificial pneumoperitoneum must not, however, be considered a routine diagnostic procedure for this kind of condition, since simple fluoroscopic and radiographic examination will permit a reasonably certain diagnosis in most cases.

Incidentally, it is occasionally impossible to separate the liver completely from the diaphragmatic sac by air insufflation, even in uncomplicated cases[10] (our case 6). This is bound to occur when the portion of the liver which is attached to the falciform ligament is drawn into the pouch; this "bare area" of the liver surface is extraperitoneal and therefore cannot be detached from the inferior surface of the diaphragm by intraperitoneal air.[40]

Among the conditions to be considered in differential diagnosis[12, 18, 37] there is one group which can easily be ruled out. They comprise those anomalies of the gastrointestinal tract producing shadows in the right cardiophrenic angle[18] which either contain gas or can be filled with barium (stomach or intestines herniated through the right foramen of Morgagni, large hiatus hernias or epiphrenic esophageal diverticula[41]). On the other hand, omentum herniated through the right foramen of Morgagni closely resembles the picture of herniated liver on simple x-ray examination,[37] but can be distinguished from it by the associated upward displacement of the colon and the stomach.[36] The diagnosis of other conditions, such as mediastinal[26] or pericardial tumors or cysts,[37] especially hydatid cysts,[4, 41] may be more difficult to establish by simple x-ray examination and may require special technics including tomography and pneumoperitoneum, for a final conclusion. The experience that most of the masses found in the cardiophrenic angle have proved to be benign[34, 37] may be reassuring in cases in which it becomes impossible to arrive at a definite diagnosis. Concerning malignant tumors of the liver, it is most improbable that these will protrude into the chest unless they develop in a preëxisting herniated portion of liver tissue.[12, 41] The same holds true for hydatid cysts,[12] as was shown in a

case [2] in which autopsy revealed a large calcified intrahepatic cyst partly occupying an accessory lobe and moulded into a typical diaphragmatic pouch.

From a review of the literature and our own observations it would appear that partial eventration of the right diaphragm with herniation of the liver will invariably show the classic findings described above and will offer no major diagnostic difficulties. Only rarely is pneumoperitoneum required for differential diagnosis.

Pathology and Pathogenesis

In surgical [1, 3, 10, 17, 18, 20, 26, 34, 42] and autopsy reports [2, 4, 6, 7, 9, 34] the affected portion of the diaphragm is described as a thin and translucent, fibrous, membranous or aponeurotic pouch, grossly free of muscle fibers

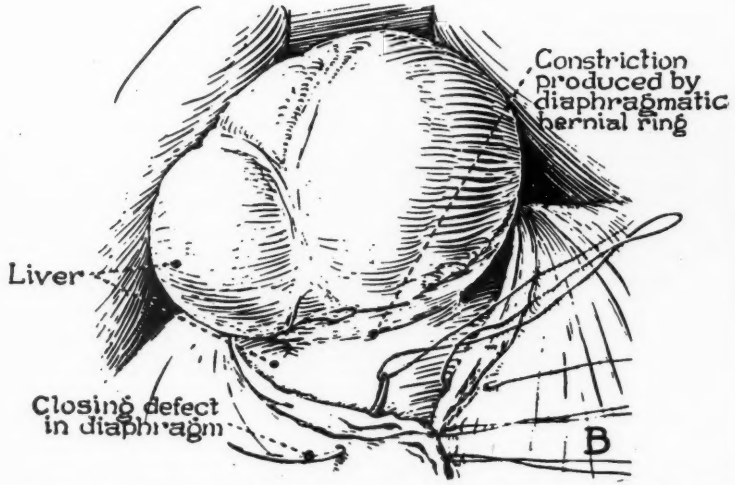

Fig. 12. Operative view of the herniated portion of the liver, shown after the removal of the sac. The formation of a pedicle by a constriction produced by the diaphragmatic hernial ring is visible. (From Clay and Henlon: Pneumoperitoneum in Diaphragmatic Hernia.[11])

and bulging into the thoracic cavity. It consists essentially of fused diaphragmatic pleura and peritoneum. The opening of the pouch is horseshoe-shaped or crescentic and bound by a band of diaphragmatic muscle. The peripheral portion of the hemidiaphragm is unaffected. Microscopically the wall of the sac reveals the two intact serosal layers, with scant intervening connective tissue and a few scattered muscle fibers. There is no actual gap in the diaphragm.

The diaphragmatic sac is occupied in its entirety by an accessory lobe

of the liver which forms a hump on its upper surface and consists of parenchyma identical with that of the rest of the organ. The base of this protuberance fits snugly into the ring-like opening of the diaphragmatic pouch. It is often broad and pedicle-like, and constricted by the muscular ring formed by the surrounding normal diaphragm [11, 27, 42] (figures 11 to 13).

The findings in infants born with this anomaly are particularly instructive. Two such cases were studied and reported by Cartellieri.[7] In both cases large gaps were also present between the pleural and peritoneal cavity, but were limited to the *left* hemidiaphragm. The right diaphragm was well developed and muscular in its posterolateral portion. In the first case it terminated sharply with a concave edge. The ventral portion of the hemidiaphragm was thin, transparent, grossly free of muscle fibers and "pouched out towards the thoracic cavity by a hump on the superior surface of the right lobe of the liver." This protuberance was sharply delineated against

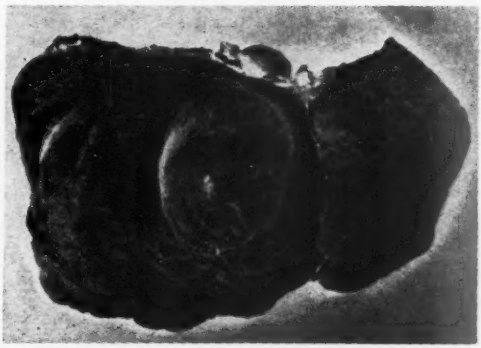

FIG. 13. Superior surface of a cirrhotic liver with a "diaphragmatic hump." (From Christie: Diaphragmatic Deformation of the Liver.[9])

the adjacent liver tissue. In the second case the right chest was almost completely taken up by a large pocket of diaphragm which contained a dome-shaped structure superimposed upon the right lobe of the liver and merging gradually into it with its posterior and lateral surface. Similar findings were reported in infants and children subjected to surgical exploration or repair of the hernial opening in the right diaphragmatic muscle.[1, 3, 17, 33]

These findings, identical as they are in the newborn and the adult, suggest that: (1) the lesion is congenital; (2) the basic pathologic disturbance is aplasia or hypoplasia of part of the musculature of the right diaphragm, usually in the antero-median, less often in the central portion; (3) the stretching and bulging of the affected portion are due to its inability to resist the physiologic intra-abdominal pressure; (4) the underlying portion of the liver prolapses into the diaphragmatic pouch as it develops and, by moulding itself into the abnormal space, forms an accessory lobe which is intrathoracic

but remains subdiaphragmatic; (5) presumably this development occurs during the intra-uterine period, although the eventration conceivably may increase during postnatal life.

The presence of the lesion at birth and in infancy and the constancy of its location characterize it as a developmental anomaly. The clue to the origin of the more common *antero-median* type of partial eventration is probably to be found in the peculiarities of the early phases of the embryonic development of the diaphragm.[30] The partition of the continuous coelom of the fetus into a thoracic and an abdominal cavity begins with the formation of the "septum transversum," a ventral shelf of mesodermal tissue. By the eighth week of fetal life the process of partition is completed by the development of paired pleuroperitoneal folds which become the dorsolateral

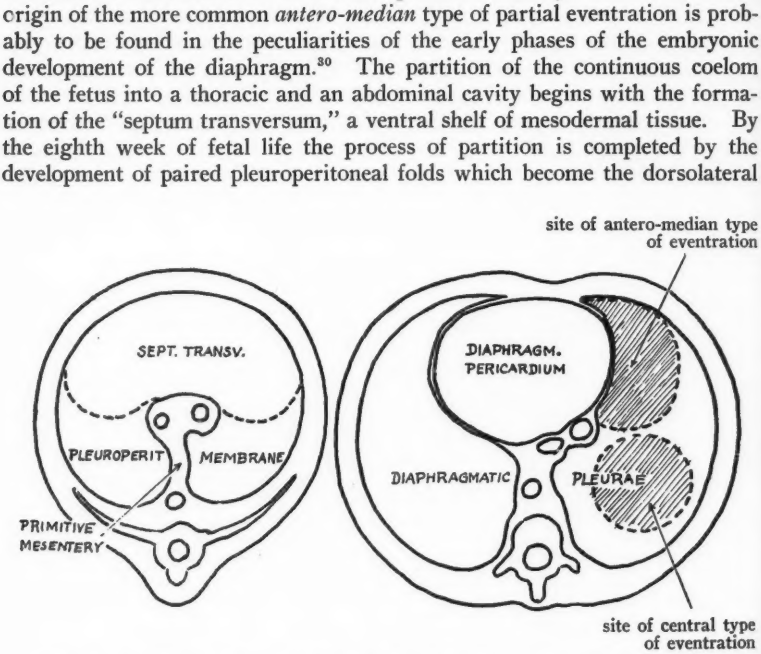

FIG. 14. Diaphragms of the fetal and the adult diaphragm indicating the relationship between the area of the embryonic septum transversum and the more common (antero-medial) site of partial diaphragmatic eventration.

parts of the future diaphragm, and their fusion with the primitive mesentery (the mediastinum) centrally and the septum transversum anteriorly. The muscular component between the pleural and the peritoneal membrane develops later and independently.[16, 21, 30] The comparison of a diagram of the primitive embryonic diaphragm and of a fully developed one (figure 14) shows that the septum transversum represents the substrate for an approximately triangular ventral portion of the fully developed diaphragm, comprising the area occupied by the diaphragmatic pericardium and a smaller adjacent area to the right of it. The latter, bordered by the heart and the anterior chest wall, is the most common site of partial eventration of the diaphragm.

The maldevelopment responsible for this anomaly could conceivably be

either (1) failure of the right pleuroperitoneal folds to fuse solidly with the septum transversum,[6] or (2) failure of muscular tissue to develop in the septum transversum.[21, 25] The former (nonfusion) appears unlikely because no actual defect is found in the pleural or peritoneal membranes. The latter possibility (muscular aplasia) appears more plausible, since absence of muscle fibers in the diaphragmatic pouch has been established in the newborn as well as in the adult. The absence of such a muscular layer is apparently of no consequence in that part of the original septum transversum which is buttressed by the overlying heart. The remaining unsupported segment to the right of the heart, however, is obviously unable to withstand the intra-abdominal pressure, becomes stretched, bulges into the chest and forms the hernial sac which, as it expands, becomes occupied by the adjacent portion of the liver. This concept of the development of the antero-median type of partial eventration of the right diaphragm is offered as a hypothesis which fits the established facts and may represent a plausible explanation for the development of the anomaly.

Outpouching of the *central* part of the right diaphragm with a corresponding hump of the liver has been seen less commonly (our case 6; case 4 of Clay[10]; case 2 of Drouet[12]; case 2 of Gudbjerg[18] and case 4 of Wagner[41]). In these cases the pouch was located in the central tendinous portion. The localized weakness of this area has been ascribed to an excessive involution of the diaphragmatic muscle during the physiologic process of formation of the central tendon.[21]

Nomenclature

The anomaly described above has become known under various names, depending mainly on the relative rôle attributed to the diaphragm and to the liver, respectively, in the pathogenesis of the lesion. It has been called *partial eventration,*[1, 24, 29, 31, 34] *circumscribed relaxation,*[18, 31] *biloculation*[16] and *congenital hernia* of the diaphragm[10, 13, 14] on the one hand, and congenital *diaphragmatic herniation of the liver*[1, 8, 33, 35] and *superior accessory or anomalous lobe of the liver*[15, 20, 22, 23, 27, 38] on the other hand. These names have been used interchangeably, as none of them has achieved any exclusive degree of popularity.

This profusion of names is confusing and likely to delay a wider acquaintance with the subject. If the term "eventration" or relaxation is to be reserved for a condition in which an entire hemidiaphragm is membranous, elevated and unable to contract on inspiration, it may be preferable to call this limited affection a congenital diaphragmatic hernia,[10, 39] which it actually is by definition (an abnormal congenital defect in the musculature of the diaphragm through which a viscus, the liver, protrudes covered by the intact serosal membrane *). Since, however, the term congenital dia-

*It differs from other nontraumatic diaphragmatic hernias (and most other abdominal hernias) in that it does not pass through a preformed hiatus or a normally existing muscular gap, but through an area weakened by muscular aplasia.

phragmatic hernia includes hernias through preformed muscle gaps, such as Bochdalek's, Larrey's and Morgagni's, the designation as *congenital diaphragmatic herniation of the liver* is suggested as the most suitable name accurately defining the nature of the lesion.

Summary

1. Six cases of partial eventration of the right diaphragm with herniation of the liver are reported.

2. The frequent occurrence of this anomaly and the importance of its differentiation from other intrathoracic, pericardial, pleural, diaphragmatic and subdiaphragmatic masses are discussed.

3. The characteristic radiologic features are described, and the use of an artificial pneumoperitoneum for final diagnosis is discussed. The latter is not regarded as an indispensable diagnostic measure.

4. Aplasia of the diaphragmatic muscle in an area derived from the embryonic septum transversum is offered as a possible explanation for the more common type of hernia of the right diaphragm which is known to exist at birth and is found regularly at the same location.

5. The term congenital diaphragmatic herniation of the liver is suggested as most appropriate for the condition.

Summario in Interlingua

Fluoroscopia thoracic demonstra a vices in le dextere angulo cardiophrenic un dense umbra semiglobular a contorno acute. Iste massa non es separabile ab le diaphragma. Illo pote mover se levemente con le diaphragma, e etiam le respiration pote poner lo in un motion paradoxe. Illo occupa communmente le portion anteromedial, plus rarmente le portion central del hemidiaphragma dextere. Iste constatation indica un congenite herniation diaphragmatic del hepate. Un parte del lobo dextere ("lobo accessori superior") protrude a in le thorace sub le copertura de un portion membranose e amuscular del diaphragma. Le roentgenogramma es usualmente satis characteristic pro permitter un diagnose definitive. Le 6 casos reportate in le presente studio illustra iste facto.

Pro decider casos dubitose on pote servir se de insufflation intraperitoneal de aere. Le diagnose es positive si iste procedimento resulta in un separation inequivoc de un gibbo super le domo del hepate ab le sacco diaphragmatic. Iste anomalia es rarmente le causa de symptomas clinic, excepte in casos ubi le herniate portion del hepate es strangulate. Normalmente le condition es un constatation coincidental, sed illo es facile a confunder con tumores intrathoracic, diaphragmatic, o subdiaphragmatic o con cystes o hernias del visceres abdominal a transverso le foramine de Morgagni.

Le lesion hic discutite ha essite trovate in infantes e adultos. Illo es probabilemente causate per aplasia muscular del triangule portion anterior del diaphragma (le "septo transverse" del feto). Le pression physiologic intra-abdominal causa un extrusion del tenuificate portion del diaphragma verso le thorace e modula le adjacente parte del hepate a in le assi-formate sacco.

Le nomine "congenite herniation diaphragmatic del hepate" es proponite como le plus appropriate description del lesion.

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BILATERAL HILAR ADENOPATHY: ITS SIGNIFICANCE AND MANAGEMENT*

By Corrin H. Hodgson, M.D., F.A.C.P., Arthur M. Olsen, M.D., F.A.C.P., and C. Allen Good, M.D., *Rochester, Minnesota*

For many years stereoroentgenograms of the thorax have been made routinely on patients who present themselves for general examination at the Mayo Clinic. Numerous abnormalities of the thorax have been disclosed by these films, among them a good many cases of bilateral enlargement of the hilar lymph nodes. The discovery of such adenopathy, especially in persons who had had no symptoms referable to the thorax and who presented no pertinent physical findings, was often a cause of surprise and alarm to the physician as well as to the patient. These potato-like hilar enlargements were sometimes considered to have serious import, and formerly at the Mayo Clinic and elsewhere it was common practice to recommend roentgen therapy for such persons, even though no histologic diagnosis had been made. Regression of the hilar enlargements, indicating apparent radiosensitivity of the lesions, was considered to be "proof" of the diagnosis of lymphoma (figures 1 and 2).

A number of years ago it became apparent that in many instances bilateral enlargement of the hilar lymph nodes regressed spontaneously. The patient's thoracic symptoms, if indeed he had any, subsided and he remained well. Thus we came to believe that a policy of giving roentgen therapy routinely in cases of bilateral hilar adenopathy not only is unnecessary but also often leads to an erroneous diagnosis of Hodgkin's disease if the adenopathy disappears after treatment. We concluded that roentgen therapy should no longer be advised for bilateral enlargement of the hilar lymph nodes unless histologic proof of a neoplastic condition is available.

Since adequate treatment of bilateral hilar adenopathy depends on correct diagnosis of the cause of the condition in the individual patient, increased knowledge of such causes is needed. In order to learn more about the causes of this type of adenopathy, especially in the accidentally discovered case, we have studied the records of patients who presented roentgenographic evidence of this abnormality and who were seen in the last seven years. This study forms the basis for this report.

Before the analysis of cases is presented, it is necessary to consider certain general features of the abnormality.

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The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

FIG. 1*a*. Bilateral hilar adenopathy as seen in 1945; adenopathy subsequently disappeared following roentgen therapy; presumptive diagnosis of Hodgkin's disease; *b*, same patient, 1953; proved sarcoidosis; Hodgkin's disease not present.

FIG. 2a. Proved lymphosarcoma with bilateral hilar adenopathy; *b*, six weeks later, showing marked improvement after roentgen therapy.

General Considerations

Etiology: As would be expected, almost any condition that causes chronic pulmonary disease can sometimes cause bilateral hilar adenopathy. The numerous causes for the condition as given by various authors are: (1) tuberculosis, (2) BCG vaccination, (3) fungus infections: histoplasmosis and coccidioidomycosis, (4) sarcoidosis, (5) pneumoconiosis, (6) lymphogranuloma venereum, (7) secondary syphilis, (8) neoplasms: Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, giant follicular lymphoma and leukemia, (9) metastatic malignant growths from the lung and elsewhere, (10) conditions associated with erythema nodosum, and (11) fibrocystic disease of the pancreas, a cause which was added after study of the present cases.

Tuberculosis is a common cause of unilateral hilar adenopathy, but infrequently a cause of bilateral hilar adenopathy. Löfgren,[1] in a study of patients with erythema nodosum attributable to tuberculosis, found that 86% had hilar adenopathy unilaterally but that only 9% had it bilaterally. Skiöld [2] noted that in 30.5% of his cases of unilateral hilar adenopathy the enlargement of the nodes was due to tuberculosis but that in none of his cases of bilateral hilar adenopathy was it due to tuberculosis. In only 7% of Ustvedt's [3] 69 cases of hilar adenopathy due to tuberculosis was the adenopathy bilateral.

Larsen [4] attributed bilateral hilar adenopathy in eight cases to BCG vaccination.

Dickson and Gifford [5] stated that bilateral hilar adenopathy occurs in patients with coccidioidomycosis, and later Goldstein and McDonald [6] found it among their 75 cases.

Furculow [7] and Prior, Saslaw and Cole [8] reported typical cases of bilateral hilar adenopathy in their articles on histoplasmosis. Prompted by their reports, we reviewed the first 21 cases of histoplasmosis seen at the Mayo Clinic, but did not find bilateral hilar adenopathy in any of them. The reason for this may be that in most of the cases the disease had passed the acute phase.

Schaumann [9] in 1913 was the first to recognize sarcoidosis as a cause of bilateral hilar adenopathy, and mentioned that such adenopathy was very common in this condition but not a constant finding. Since that time sarcoidosis has been recognized by numerous investigators as one of the most common causes of bilateral hilar adenopathy.

The neoplasms of the lymphoma group and metastatic malignant growths are well substantiated as causes of bilateral hilar adenopathy. Erythema nodosum and its relationship to such adenopathy will be discussed later.

The remaining causes of bilateral hilar adenopathy are so unusual or unimportant as to require no further mention.

Symptoms: Most patients with bilateral hilar adenopathy have no symptoms from the adenopathy, but others have a few minor complaints such as

slight cough. There may be some distortion or compression of the bronchi from the enlarged nodes, but only occasionally is there obstruction or bronchial invasion by the process involving the nodes; therefore, severe cough, hemoptysis and excessive sputum are not common. A few patients complain of pain in the sternal area or over either lung. In general, however, the symptoms are those of the systemic process rather than of the adenopathy itself. Two interesting conditions that frequently are associated with bilateral hilar adenopathy are arthritic symptoms and erythema nodosum, their importance to the subject demanding special consideration.

Articular Symptoms: The articular symptoms associated with different forms of pulmonary disease are little understood. They occur frequently in patients with bilateral hilar adenopathy. Ustvedt [3] noted articular symptoms in 26% of 77 patients with such adenopathy, four fifths of those with articular symptoms also having concurrent erythema nodosum. Löfgren,[10] in his series of 212 cases of "bilateral hilar lymphoma syndrome" (large, rather symmetric hilar adenopathy and a negative or weak to moderate tuberculin reaction), recorded articular symptoms in 18.2% of the group without erythema nodosum but in 89% of the group with erythema nodosum. Skiöld,[2] in studying patients with erythema nodosum and erythema multiforme, noted articular symptoms in 44.4% during the time of the skin eruption. He stated that the joint ailments are most common in the cases of bilateral hilar processes, and less frequent in tuberculosis and other conditions without bilateral hilar adenopathy.

It can be said, therefore, that articular ailments are common in patients with bilateral hilar adenopathy, are even more common in patients with erythema nodosum, but attain high frequency when bilateral hilar adenopathy and erythema nodosum occur together.

The large joints (knees, wrists, ankles, elbows) are more frequently involved than the smaller joints, according to Skiöld.[2] He reported that he had not seen a single case of migratory joint involvement, and noted that the joint symptoms never remain after the skin lesions fade but that they may recur with new crops of efflorescence.

Erythema Nodosum: Any discussion of bilateral hilar adenopathy must necessarily include a consideration of its relation to erythema nodosum. The percentage of patients with erythema nodosum who are found to have an associated bilateral hilar adenopathy is given by various authors as follows: Johnson, Hanson and Good,[11] 8%; Spink,[12] 6.2%; Löfgren,[1] 16.8%; Sosman, Bailey and Armstrong,[13] 19.5%; Skiöld,[2] 9.9%; Ustvedt,[3] 6%; and Favour and Sosman,[14] 9.2%. Conversely, the incidence of patients with bilateral hilar adenopathy who also have erythema nodosum is given by Löfgren and Lundbäck [15] as 53.3% in their 212 patients with "bilateral hilar lymphoma syndrome," and by Ustvedt [3] as 35% in his 77 patients with bilateral hilar adenopathy. This information definitely establishes a significant association between bilateral hilar adenopathy and erythema nodosum but does not clarify the cause of the association.

Erythema nodosum has been attributed to many causes: streptococcal, virus and other infections; dental infection; respiratory infections of various kinds; gonococcal infection; meningococcal infection; measles; herpes zoster; lymphogranuloma inguinale; ringworm of the scalp; leprosy; rheumatic fever; primary and secondary tuberculosis; chronic ulcerative colitis; coccidioidomycosis; sarcoidosis; drug sensitivity (sulfonamides, bromides, iodides, thiouracil); and multiple concurrent infections. It is noteworthy that almost no one associates erythema nodosum with malignant disease. It was not present in any of Ustvedt's 14 cases of bilateral hilar adenopathy due to malignant disease. Goldstein [16] reported one case of erythema nodosum and lymphosarcoma, to his knowledge the only one ever reported. Though erythema nodosum sometimes occurs in patients with malignant disease, nevertheless the combination of all three—erythema nodosum, bilateral hilar adenopathy and malignant disease—must be extremely rare. Therefore it is perhaps justifiable to conclude that bilateral hilar adenopathy is not likely to be due to malignant disease when erythema nodosum is also present.

The manifestations represented by the term "erythema nodosum and bilateral hilar adenopathy" may be due to a number of different causes, and hence the term should not be considered to represent a clinical entity in itself, else important specific causes may easily be overlooked.

Physical Findings: Careful examination of the patient with bilateral hilar adenopathy often yields significant diagnostic information, such as splenomegaly, enlargement of lymph nodes suitable for biopsy, lesions of the skin and mucous membranes, evidence of primary malignant lesions, and joint manifestations. The hilar adenopathy itself causes no unusual signs. Venous obstruction of the innominate vein or superior vena cava is almost unknown in the benign forms of bilateral hilar adenopathy, but may be present in advanced lymphoma or metastatic malignant disease. Dyspnea and cyanosis are generally minimal unless extensive malignant invasion has taken place or the lungs are significantly involved. Signs of serious disease, such as wasting, anemia, fever and debility, are quite significant in distinguishing malignant from benign forms of bilateral hilar adenopathy, as will be seen later.

Diagnosis: The usual laboratory procedures are seldom of much help in making a diagnosis. Significant anemia, however, suggests a more serious process, and if leukemia is present the hematologic findings should be diagnostic. Complement-fixation tests are sometimes used as aids in the diagnosis of coccidioidomycosis and histoplasmosis, but the final diagnosis rests on recovery of the organism.

Skin tests may be helpful. Properly applied and interpreted, the tuberculin test is at times of value in the study of bilateral hilar adenopathy. A recent change in the reaction from negative to positive suggests a diagnosis of primary tuberculosis, but a negative reaction is strong evidence against

such a diagnosis. However, a positive reaction to a single tuberculin test is not necessarily evidence that the bilateral hilar adenopathy is due to tuberculosis, nor is a positive reaction a sound basis for saying that the adenopathy is not due to sarcoidosis. Coccidioidin and histoplasmin skin tests are of scientific interest, but the same degree of accuracy does not seem to obtain with these as with tuberculin tests, and thus their value in clinical diagnosis is limited. Skin tests should be considered as offering corroborative but not conclusive diagnostic evidence.

Cultures of gastric washings, sputum, bronchial secretions, pleural fluid and tissue are very important in the detection and exclusion of tuberculosis, fungous diseases and other infections. It is to be emphasized that bacteriologic investigation of granulomatous tissue is fully as important as microscopic examination of tumor tissue.

The roentgenographic aspects of diagnosis will be covered later in the analysis of cases.

Cytologic examination of body fluids, particularly sputum, bronchial secretions and pleural fluid, sometimes may lead to a diagnosis of malignant disease.

Biopsy is the most useful single procedure in the diagnosis of bilateral hilar adenopathy. It may be performed on palpable nodes, skin lesions, tonsils, sternal marrow, lesions seen on bronchoscopy, and the liver; occasionally direct biopsy of the lung may be performed. Biopsy of the hilar nodes by means of transbronchial needle puncture has inherent dangers which contraindicate its use.

Lymph node tissue for biopsy is most commonly obtained by exploration of the supraclavicular space. Frequently the cervical, supraclavicular or jugular nodes are palpable, but when they are not, exploration of the supraclavicular space often results in the removal of tissue from which a diagnosis can be made. Unless the diagnosis is more readily made otherwise, the supraclavicular space should be explored in all cases, whether or not palpable nodes are present. From purely anatomic considerations, it would seem preferable to explore the right supraclavicular space before the left when no nodes are palpable. The surgeon should explore not only the supraclavicular fat pad but also the jugular nodes and those along the trachea.

Ordinarily, bronchoscopy is not indicated in bilateral hilar adenopathy. The indications for it are the same as in any other condition, but it need not be performed simply because of the adenopathy unless signs of bronchial obstruction or hemoptysis are present. Löfgren and Lundbäck [15] obtained biopsy diagnoses in five of the 23 cases of "bilateral hilar lymphoma syndrome" in which they performed bronchoscopy.

Analysis of Cases

The cases included in this study are not consecutive ones, and they probably constitute only a small part of the cases of bilateral hilar adeno-

FIG. 3a. Sarcoidosis with bilateral hilar adenopathy as proved by bronchoscopic biopsy in 1941; *b*, eggshell calcification of hilar nodes as evident in 1949.

pathy seen at the Mayo Clinic during the period covered; hence, because of the method of selection, they cannot be analyzed statistically as a representative series.

Roentgenologic Aspects: As we have indicated, the cases included in this series were selected solely on the basis of unmistakable roentgenographic evidence of bilateral enlargement of the hilar nodes. Usually evidence of this enlargement was apparent in the postero-anterior stereoroentgenograms made as a routine part of the general examination. Infrequently, the evidence of such enlargement was gained from body-section roentgenograms or those made with a grid. In the selection of cases all degrees of nodal enlargement were seen. In borderline cases the presence or absence of bilateral hilar adenopathy was determined by the judgment of three examiners, rather than by that of one individual. Cases were rejected if any one of the examiners doubted the presence of bilateral nodal enlargement.

In most instances the enlarged nodes cast discrete shadows which were round, oval or lobulated. In the majority of cases the degrees of enlargement on the two sides were symmetric, but this was not a requisite for selection. Also, in the majority of cases there was concomitant enlargement of some of the nodes in the mediastinum. Most frequently affected were those in the chain lying along the right side of the trachea, the so-called right paratracheal nodes. Less frequently the left paratracheal nodes were enlarged, and in a few instances the mediastinum was widened bilaterally.

In some instances parenchymal lesions were seen in addition to bilateral hilar adenopathy, but their presence or absence did not influence the selection of cases. Such a lesion may not be evident roentgenographically at the time bilateral hilar adenopathy is discovered and yet be seen in subsequent films. Since the diagnosis of hilar enlargement still obtained regardless of the presence or absence of parenchymal lesions, it was not thought advisable to exclude such cases from study. Among the entities noted were (1) disseminated tiny nodules, (2) disseminated reticular fibrosis, (3) unilateral or bilateral patches of consolidation, and (4) unilateral or bilateral areas of fibrosis.

Although calcification was present in the region of the hilus of the lung in some cases, the swollen nodes which caused the bilateral hilar adenopathy were not calcified. In some instances calcification was seen also in the mediastinum, but, again, not in any of the enlarged nodes. In one case of histologically proved sarcoidosis [17] (figure 3), eggshell calcification developed in the hilar nodes after the primary swelling had subsided. This has been reported to occur in cases of silicosis, but this instance represents the authors' first experience with such a phenomenon in sarcoidosis.

Critical study of the roentgenograms in this series of cases of bilateral hilar adenopathy revealed no characteristic which would distinguish between neoplastic and non-neoplastic conditions. The nodal swelling frequently

regressed or completely disappeared in patients with benign disease (figures 1, 4 and 5), but similar regression was noted also after roentgen therapy in cases of lymphoma (figure 2). For this reason roentgen therapy should be withheld until a specific diagnosis has been made by histologic examination.

Spontaneous regression was observed after serial roentgenographic examination in many instances of sarcoidosis and in cases in which no specific diagnosis could be made. In no case of malignant involvement did the bilateral hilar adenopathy subside without treatment.

Bilateral hilar adenopathy must be differentiated from bilateral enlargement of the hilar shadows caused by engorgement of the vessels in this region. This distinction can be made in most instances by roentgenoscopy. In the unusual case it may be necessary to employ angiocardiography.

Features According to Cause of Adenopathy: Although the patients included in this study were not selected in a manner to allow statistical analysis, they did present certain significant features when studied from the standpoint of groups based on the proved cause of the adenopathy.

Indeterminate Disease: There were 46 patients with bilateral hilar adenopathy for whom no diagnosis was made. Their ages ranged from 16 to 64 years, the average being 40.9 years. Only one patient was less than 20 years old. Twenty-three were males and 23 were females.

The outstanding characteristic of this group was the apparent good health of nearly all the patients. Ten were found to have bilateral hilar adenopathy on purely routine roentgenographic examination of the thorax, and these were in good health. In a number of other cases the adenopathy was found in the course of examination for entirely unrelated, not serious disorders. Thirteen of the 46 patients had joint symptoms, and nine also had erythema nodosum. All the latter nine patients were among the 13 with joint manifestations.

Only two of the patients are known to have died, one from cerebellar infarction after three years and the other from an unknown infectious granuloma after three weeks. Necropsy in both cases failed to demonstrate a malignant tumor or tuberculosis. Of 32 other patients seen more than one year prior to this report, 28 were available for some type of follow-up; these 28 patients were known to be living and in almost all cases were well more than two years, on the average, after admission. As in the sarcoid group, to be described later, their apparent good health seemed to be an important point in differentiating this group from the group of patients with malignant disease, almost all of whom were obviously ill.

Roentgenographic clearing of the bilateral hilar adenopathy was a matter of interest. Follow-up roentgenograms were available in 31 of the 46 cases. In 24 of these, subsequent x-ray examination demonstrated that the bilateral hilar adenopathy had cleared completely, while in seven others it was still present. The adenopathy was seen to subside in as short a time as two months after discovery and, conversely, to persist after eight years.

The adenopathy disappeared within five months.

FIG. 4.

FIG. 5.

FIG. 4. Sarcoidosis proved by supraclavicular biopsy. Erythema nodosum was present. Bilateral hilar adenopathy disappeared within six months without treatment.

FIG. 5. No proved diagnosis in this case, in which erythema nodosum, articular symptoms and bilateral hilar adenopathy were present. The adenopathy disappeared within five months.

Paratracheal lymph nodes were enlarged on the right side alone in 17 cases, on the left side alone in one case, and bilaterally in five cases. Parenchymal involvement of the lungs was present in 11 of the 46 cases.

A number of the patients had been informed that they had Hodgkin's disease, but they had no clinical or pathologic evidence favoring such a diagnosis except the bilateral hilar adenopathy. They subsequently remained well, without developing other evidence of that disease.

This group of 46 patients resembled the sarcoid group, to be considered next, as to age, general good health at the time of examination and follow-up, and tendency to spontaneous regression. It is conceivable that many of them had sarcoidosis. There was nothing to suggest malignant disease or tuberculosis as a possible cause of bilateral hilar adenopathy in this group.

Without knowledge as to the cause of the bilateral hilar adenopathy in these patients, no specific therapy was to be recommended.

Sarcoidosis: There were 44 patients with bilateral hilar adenopathy due to proved sarcoidosis. Their ages ranged from nine to 70 years, with only two being less than 20. The average age was 43. Eighteen were males and 26 were females. All of them underwent biopsy, usually of lymph nodes or skin, which disclosed the histologic characteristics of sarcoidosis, and all presented clinical findings consistent with that diagnosis. Bacteriologic studies were performed on the tissue wherever possible.

An outstanding characteristic of this group was the apparent good health. Very few of the patients appeared to be suffering from serious or progressive disease, and most of them subsequently continued in good health. Ten of the 44 patients had joint symptoms and three had erythema nodosum. Two of these three were among those who also had joint symptoms.

Thirty-five of the 44 patients were seen more than one year prior to this report, and all of these were available for follow-up. They were alive an average of 4.4 years after detection of bilateral hilar adenopathy. The apparent good health encountered at the time of examination of sarcoid patients with such adenopathy seems to be important in distinguishing them from patients with malignant disease, most of whom appear ill.

Three of the 44 patients died. One of the deaths occurred from suicide two years after diagnosis of sarcoid, the second from sarcoidosis after four years, and the third from undetermined cause after nine years.

It seemed desirable to determine the frequency with which bilateral hilar adenopathy occurs in sarcoidosis, and for this information a group of 194 Mayo Clinic cases of proved sarcoidosis studied by Carr and Gage [18] was reviewed; Dr. A. H. Holt is presently reviewing the group from the roentgenographic standpoint. Although there may be more, 21 definite cases of bilateral hilar adenopathy were found, representing 10.8% of the entire group. It seems safe to say, therefore, that at least 10%, perhaps more, of all patients with sarcoidosis have bilateral hilar adenopathy. If serial roentgenograms had been taken in all cases, undoubtedly a higher incidence

would have been noted. According to Löfgren and Lundbäck, Dressler [19] found bilateral hilar adenopathy in 47 of 67 patients with sarcoidosis.

We also sought to determine how soon bilateral hilar adenopathy may clear up in sarcoidosis and how long it may persist. No x-ray follow-up was available in 17 of the 44 cases of the present series. In 18 cases x-ray examination showed that the bilateral hilar adenopathy had cleared up. In nine other cases the last follow-up roentgenograms showed that the bilateral hilar adenopathy persisted, but in some of these the follow-up was for only three months. From a study of these cases it can be said that bilateral hilar adenopathy due to sarcoidosis may clear up in less than six months from the time of discovery, or it may persist for more than six years.

Enlarged paratracheal nodes were present on the right side alone in 23 cases, on the left side alone in one case, and bilaterally in six cases. Parenchymal involvement of the lungs was present in 12 of the 44 cases. It consisted of a diffuse, finely nodular "fibrosis" in eight cases, and of "pneumonitis" in four. Bilateral pleural effusion was noted in one case.

Several patients with sarcoidosis had been told erroneously that they probably had Hodgkin's disease, and x-ray therapy had been suggested or had actually been given them (figure 1). Now a correct diagnosis can and should be made in the great majority of such cases. An erroneous diagnosis of lymphoma is a real tragedy for the patient because of the grave prognosis, whereas a correct diagnosis enables one to inform the patient of the hopeful nature of sarcoidosis.

In spite of the many forms of therapy recommended in the past, there is as yet no specific treatment for sarcoidosis.

Lymphoma and Leukemia: The initial reason for undertaking this study was to investigate the relationship of bilateral hilar adenopathy to the lymphomas. Eleven cases of such adenopathy due to malignant lymphoma were studied. Nine of these were found in a review of the thoracic roentgenograms in 100 consecutive cases of histologically proved lymphoma of various types, and in all nine there was unequivocal bilateral hilar adenopathy. This probably represents fairly accurately the frequency with which such adenopathy occurs in this condition.

In a review of the histories of the 11 patients with lymphoma it was apparent that they were ill of serious progressive disease. All of them had abnormal lymph nodes or skin lesions easily accessible for biopsy, and it was therefore not difficult to make the diagnosis. It would seem that by the time Hodgkin's disease or lymphosarcoma produces bilateral hilar adenopathy, the process is so advanced that diagnosis should be quite easy. The roentgenographic appearance of the adenopathy in most of these cases was indistinguishable from that of sarcoidosis. Three of the 11 patients also had enlargement of the right paratracheal nodes, and one had bilateral paratracheal node enlargement. One patient had parenchymal pulmonary

disease. None of the 11 patients was said to have had joint symptoms or erythema nodosum.

The treatment of such patients is the treatment of lymphoma in general, with special emphasis on x-ray therapy of the hilar nodes. It seems apparent that x-ray therapy should not be given to patients with bilateral hilar adenopathy until the diagnosis has been proved. The diagnosis of lymphoma should be made on the basis of histologic examination of tissue only,

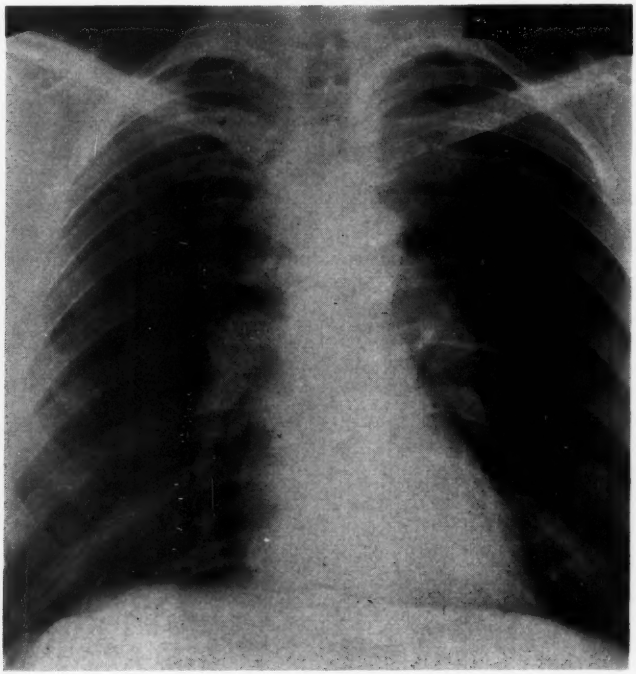

FIG. 6. Bilateral hilar adenopathy with involved right paratracheal lymph nodes. Metastatic adenocarcinoma was present.

and not on the basis of response to x-ray therapy, as this frequently leads to error.

Because bilateral hilar adenopathy is said to occur in patients with leukemia, the thoracic roentgenograms in 100 consecutive cases of various types of proved leukemia were reviewed but in none was bilateral hilar adenopathy found. This does not rule out the possibility of its occurrence, but indicates its infrequency.

Metastatic Malignancy: There were six cases of bilateral hilar adenopathy due to metastatic lesions. The adenopathy was attributable to ma-

lignant melanoma in one case, to carcinoma of the prostate in two, and to malignancy of unknown origin in three. The roentgenographic appearance of the bilateral hilar adenopathy due to malignant causes may be indistinguishable from that due to benign conditions such as sarcoidosis (figure 6). Neither joint manifestations nor erythema nodosum was noted in these six patients.

Miscellaneous Diseases: Bacteriologically proved tuberculosis was present in only one patient with bilateral hilar adenopathy, emphasizing that the two conditions may be associated but that the association is perhaps unusual. After three months of treatment with 1 gm. of dihydrostreptomycin given

FIG. 7. Fibrocystic disease of the pancreas. Bilateral hilar adenopathy and bilateral pneumonia were present.

three times weekly, 16 gm. of sodium para-aminosalicylic acid given daily, and 300 mg. of isonicotinic acid hydrazide given daily, there was considerable decrease in the size of the hilar nodes and the patient was much improved clinically. This case emphasizes the need for accurate diagnosis of conditions requiring special treatment.

Silicosis, some emphysema and rather marked bilateral hilar adenopathy were found in one patient, a 53 year old man who had been a molder in a foundry for 30 years.

Fibrocystic disease of the pancreas was diagnosed in a four year old

girl who had had repeated attacks of pneumonia (figure 7). Bilateral hilar adenopathy was present, with areas of pneumonic consolidation in both lungs. This adenopathy persisted for at least three months, indicating chronicity. This case merely serves to emphasize that bilateral hilar adenopathy can occur in almost any chronic condition of the lungs.

None of these three patients had joint symptoms or erythema nodosum.

Summary and Conclusions

Bilateral hilar adenopathy is due to a number of different conditions, both benign and malignant, some of which require specific therapy. Tuberculosis, often a cause of unilateral hilar adenopathy, is seldom a cause of bilateral enlargement. Sarcoidosis is one of the most frequent causes of the condition. In 100 cases of lymphoma there were nine cases of bilateral enlargement of the hilar nodes. The correct diagnosis can now be made in most cases of bilateral hilar adenopathy, and should be made in every case if possible.

Because rapid regression of hilar nodes occurs spontaneously in some benign conditions, similar regression following x-ray therapy cannot be considered valid "proof" that the patient is suffering from Hodgkin's disease. X-ray therapy should be used only in cases of histologically proved malignant disease.

Erythema nodosum and articular symptoms are frequently associated with bilateral enlargement of the hilar lymph nodes. "Erythema nodosum and bilateral hilar adenopathy" do not constitute a specific entity and should not be so considered. When bilateral hilar adenopathy is accompanied by erythema nodosum it is unlikely to be attributable to a malignant disease.

The prognosis in bilateral hilar adenopathy is dependent upon the specific cause and is often very hopeful. Treatment should be directed at the specific cause of the condition.

Summario in Interlingua

Adenopathia hilar bilateral resulta de un numero de conditiones, tanto benigne como etiam maligne, alicunes del quales require un therapia specific. Tuberculosis, que es frequentemente le causa de adenopathia hilar unilateral, es rarmente responsabile pro un allargamento bilateral. Sarcoidosis es un del plus frequente causas de adenopathia hilar bilateral. Inter 100 casos de lymphoma nos constatava 9 casos de allargamento bilateral del nodos hilar. Le correcte diagnose es hodie possibile in le grande majoritate del casos.

Proque un rapide regression del nodos hilar occurre spontaneemente in certe benigne conditiones, le occurrentia de un regression post roentgenotherapia non representa un valide "prova" que le patiente suffre del morbo de Hodgkin. Roentgenotherapia deberea esser usate solmente in casos in que le malignitate del morbo ha essite demonstrate per examines histologic.

Erythema nodose e symptomas articular es frequentemente associate con allargamento bilateral del hilar nodos lymphatic. "Erythema nodose plus adenopathia hilar bilateral" non es un entitate specific e non deberea esser considerate como tal. Quando

adenopathia hilar bilateral es accompaniate de erythema nodose, il non es probabile que illo pote esser attribuite a un morbo maligne.

Le prognose in adenopathia hilar bilateral depende del causa del morbo e es frequentemente multo bon. Le therapia deberea visar al causa specific del condition.

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HEMODYNAMIC CHANGES FOLLOWING ACUTE MYOCARDIAL INFARCTION USING THE DYE INJECTION METHOD FOR CARDIAC OUTPUT DETERMINATION *

By JAMES F. GAMMILL, M.D., *Darien, Connecticut,* J. JERROLD APPLEGARTH, M.D., *San Francisco, California,* CHARLES E. REED, M.D., *Corvallis, Oregon,* JOHN D. FERNALD, M.D., *Needham Heights, Massachusetts,* and ARTHUR J. ANTENUCCI, M.D., F.A.C.P., *New York, N. Y.*†

QUANTITATIVE studies of hemodynamic changes following acute myocardial infarction in patients have not been performed until recent years,[1] and the over-all experience is quite limited.[2, 3, 4] In this series of 39 patients the diagnosis of acute myocardial infarction was clearly established from review of the history, physical findings and serial electrocardiograms. The dye injection method of determining cardiac output as described by Hamilton and associates [5, 6] was used, since it had been established that this was a safe and reliable method and could be performed without interfering with therapy and without moving the patient from his bed. In the comparison of values for cardiac output obtained by the dye injection method with those obtained in the same patients by cardiac catheterization and the Fick principle, Hamilton et al.[5] and Werko et al.[7] observed good correlation between the two methods, with no consistent or significant differences in results. A total of 96 cardiac output determinations was performed during the hospitalization of the 39 patients in this series, and 54 determinations were made on 37 patients within 67 hours after onset of infarction as judged from the history.

METHODS OF STUDY

All studies were performed at the bedside, with the patients supine and resting quietly. The femoral artery was punctured under procaine anesthesia with a No. 18 Cournand-type indwelling needle. Approximately 10 mg. of Evans blue dye (T-1824, 2 c.c. of 0.5% solution) were injected as rapidly as possible into an antecubital vein, using a specially marked 3 c.c. tuberculin syringe and a No. 18 needle. The exact amount of dye had been predetermined by quantitative weighing, with correction made for the dead space of the needle. The time interval from the injection of dye to starting the collection of blood samples was usually about 12 seconds, but we varied this from 8 to 25 seconds according to the clinical condition of the patient,

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From the Division of Medicine, The Roosevelt Hospital, New York, N. Y.
† With the technical assistance of THERESA LO PRESTI, B.S.

and usually selected an interval several seconds less than the arm-to-tongue circulation time.

A silicone-coated polyethylene tubing (2 mm. internal diameter and 52 cm. length) was used to deliver the blood to the collecting apparatus. Just prior to the procedure the tubing was rinsed with heparin-fluoride mixture (equal parts of sodium heparin solution, 10 mg. in 1 c.c., and of saturated solution of sodium fluoride) to inhibit clotting of the blood samples. In the majority of cases it required between 4 and 7 seconds for the blood to flow through the tubing. The collecting apparatus [8] consisted of a silicone-coated lucite disc 30 cm. in diameter which was rotated by a rheostat-controlled constant speed motor. Along the periphery of the disc were 32 contiguous funnels, and a 10 by 75 mm. silicone-coated Pyrex test tube was mounted by a clip beneath each funnel. The speed of revolution of the disc was measured with an ink-writing 0.2 second interval timer on a paper disc attached to the top of the lucite disc. There was usually about 0.75 c.c. of blood collected in each test tube (this varied from 0.3 c.c. to 2.0 c.c.), with a time interval of about 1.5 seconds between tubes (range of 1.0 to 3.0 seconds).

The blood samples were centrifuged at 3,500 r.p.m. for 5 minutes, the serum was pipetted into a clean set of test tubes, and it was centrifuged again for another 5 minutes. Each serum sample was then placed in a micro-cuvette and the concentration of dye was determined in a Beckman model DU quartz spectrophotometer at 610 μ wave length, being read against a sample of serum obtained prior to the injection of dye. Within the range of dye concentrations employed there was a linear relationship between optical density and dye concentration. Under these conditions an optical density reading of .48 corresponded to a dye concentration of 5 mg. per liter.

Plasma flow was calculated according to the method of Hamilton et al.[5] Blood flow was calculated from the equation:

$$\text{Blood flow} = \frac{\text{Plasma flow}}{1 - \text{corrected hematocrit}}.$$

The hematocrit was corrected for plasma trapped around the packed red cells by multiplying the observed hematocrit value by 0.96, as recommended by Gregerson.[9] Stroke volume was calculated by dividing the cardiac output by the heart rate.

Total peripheral resistance [10] in dynes sec./cm.^{5} was calculated from the equation:

$$\text{Total peripheral resistance} = \frac{\text{Mean blood pressure (mm. Hg)} \times 1.332 \times 60}{\text{Cardiac output (liters/minute)}}.$$

Arterial blood pressure was measured with a standard sphygmomanometer with an arm cuff. Mean blood pressure was approximated by choosing the mid point between diastolic and systolic pressures.

Venous pressure was measured with isotonic saline or with 5% glucose in water, with the zero reference position taken as 10 cm. above the back of the supine patient. Arm-to-tongue circulation time was measured using 5 c.c. of 20% Decholin-Sodium (sodium dehydrocholate) intravenously. The dye appearance time was measured from the time of injection to the earliest appearance of dye at the femoral artery. The mean circulation time of dye was measured from the time of injection until one-half of the injected dye had passed the point of collection for its first circulation.

Central volume, which represents the largest volume in which the dye is distributed at any instant during its first circulation, was calculated according to the method described by Newman et al.[8] System volume was calculated by multiplying the mean circulation time by the cardiac output.[6]

Five additional blood samples were drawn at 1 or 2 minute intervals starting 10 minutes after the dye had been injected. The concentration of dye in the serum of these samples was used to estimate the plasma volume of the patient, since the amount of dye available for mixing with the total blood volume was known.[9] The amount of dye injected minus the amount lost during the collection of blood samples for determining the cardiac output was the amount available for mixing with the total blood volume. The amount of dye lost during the procedure for the cardiac output determination averaged 11% (range: 5 to 19%). The total blood volume was calculated by dividing the plasma volume by (1 — corrected hematocrit).

Description of Patients Studied

The average age of the 37 male patients in this series was 55 years (range from 33 to 77 years), and the average body surface area was 1.80 square meters (range from 1.45 to 2.16 sq. M.). The two female patients were 58 and 63 years of age and had a body surface area of 1.74 and 1.39 sq. M. All of the patients with the exception of one entered the hospital with the chief complaint of severe and persistent pain in the chest, and 22 of these patients described radiation of the pain to one or more of the following locations: shoulders, arms, back or neck. Gastrointestinal symptoms consisting of nausea or vomiting accompanied the onset of the infarction in 16 patients and occurred prior to their receiving any medication. Sixteen patients had experienced one or more transient episodes of pain in the chest in the two weeks immediately preceding the clinical onset of the acute myocardial infarction.

A careful history of the past health and illnesses of these patients disclosed that 19 had had definite evidence of previous coronary artery disease, i.e., they had experienced angina pectoris for more than two months prior to admission, or had a history of a previous acute myocardial infarction. Four patients had sustained two or more acute myocardial infarctions prior to the present episode. Eleven patients, including the two with delayed hospitalization, gave a history of known hypertension; and four patients, including one with delayed hospitalization, had been taking a digitalis prepa-

ration regularly for more than five months because of previous cardiac failure. Two patients had known diabetes mellitus, and a third case of diabetes was discovered during the present hospitalization. There was an incidence of two cases of each of the following diseases: pulmonary tuberculosis, syphilis, peptic ulcer and chronic alcoholism; and one case of nephritis and one of bronchial asthma.

TABLE 1

Criteria for Clinical Grouping of Patients with Acute Myocardial Infarction Who Were Studied Within 67 Hours Following the Clinical Onset of Infarction

Group I (*least severe*)

All patients must have:

1. Pulse pressure of 36 mm. Hg or greater.
2. Mean blood pressure of 86 mm. Hg or greater.
3. Heart rate of 92 per minute or less (after bed-rest).
4. Diastolic blood pressure of 65 mm. Hg or greater.
5. Regular sinus rhythm of heart beat.

AND

Must not have:

1. Decrease in pulse pressure greater than 16 mm. Hg from time of admission until time of study.
2. Decrease in mean blood pressure greater than 29 mm. Hg from time of admission until time of study.
3. Significant bilateral râles.

Group II (*intermediate*)

All patients not included in groups I or III.

Group III (*most severe*)

All patients with any one of the following:

1. Pulse pressure of 18 mm. Hg or less.
2. Mean blood pressure of 70 mm. Hg or less.
3. Decrease in pulse pressure of 28 mm. Hg or more from admission until time of study.
4. Decrease in mean blood pressure of 35 mm. Hg or more from admission until time of study.
5. Pulmonary edema during previous 12 hours.

OR

All patients with any two of the following:

1. Pulse pressure between 19 and 30 mm. Hg.
2. Decrease in pulse pressure of 19 to 27 mm. Hg from time of admission until time of study.
3. Presence of diastolic gallop and significant bilateral râles.
4. Heart rate of 108 or greater after bed-rest.

The localization of the acute myocardial infarction as judged from serial electrocardiograms was as follows: nine patients with anterior wall involvement, eight with posterior, six posterolateral, four anteroseptal, four anteroseptal-lateral, three anterolateral, two anterolateral-posterior, one anteroposterior, one posteroseptal-lateral, and one patient in whom the location of the infarction was not recorded, and the electrocardiogram was not available for review.

Classification of Patients

After all of the physiologic measurements had been performed an extensive review of the clinical records and electrocardiograms was made in an effort to find any measurements or observations which would correlate with the level of cardiac output and stroke volume. If such correlations could be found they would be of value in judging the future treatment of patients with acute myocardial infarction. In the 37 patients studied within 67 hours after the clinical onset of the acute infarction, it was found that those who had sustained the most marked fall in pulse pressure, or in mean blood pressure, or had been in pulmonary edema, showed the lowest average values for cardiac output and stroke volume. These low values were also observed in patients who had had a less severe fall in pulse pressure or mean blood pressure and who also showed certain other signs of impaired cardiac function, i.e., bilateral pulmonary congestion and a diastolic gallop, or a tachycardia greater than 108 per minute after bed-rest. Conversely, patients who did not develop cardiac arrhythmias or pulmonary congestion or a heart rate

Table 2

Distribution According to Clinical Group of the 54 Studies Made on 37 Patients Within 67 Hours of Onset of Infarction

		Group I	Group II	Group III
17 patients with two studies	First study	4	6	7
	Second study	2	4	11
Twenty patients with one study		7	6	7
Number of observations in each group		13	16	25

exceeding 92 per minute at bed-rest and who maintained as a minimum the following blood pressure measurements: pulse pressure, 36 mm. Hg, and mean and diastolic blood pressures of 86 and 65 mm. Hg, respectively, showed the highest average values for cardiac output and stroke volume. On the basis of these findings the patients were classified in one of three clinical groups: group I, those with the least changes; group III, those with the greatest fall in mean blood pressure, pulse pressure, etc.; group II, those who showed changes of intermediate degree. The exact criteria used in this classification are listed in table 1. This grouping is not to be confused in any way with the functional and anatomic classification of patients with heart disease as standardized by the American Heart Association, since certainly all of the patients in this series would be classified as IV E under this latter classification at the time of these studies.

All 37 patients were hospitalized within 20 hours of the onset of their infarction, and the first cardiac output determination was made within 39 hours of the clinical onset of the infarction. Seventeen patients had a

second determination within 67 hours of the onset of their illness. There was an average of 23.6 hours (range, 14 to 48 hours) between the first and second studies. The data from each of these 54 separate studies are placed in one of the three clinical groups according to the findings of the physical

TABLE 3

Data Obtained in 54 Determinations on 37 Patients Within 67 Hours of Onset of Acute Myocardial Infarction

(First and Second Studies)

Summary of Data by Clinical Groups					Comparison of Groups		
	Group	Mean Value	Range of Values	Standard Error of Mean		Difference in Means	Ratio of Difference To Its Standard Error
Stroke volume (c.c.)	I	104	74–152	5.4	I vs. II	32	5.70‡
	II	72	51–87	2.7	II vs. III	19	4.70‡
	III	53	22–79	2.8	I vs. III	51	9.48‡
Cardiac output (L./min.)	I	7.70	5.04–12.19	0.54	I vs. II	2.01	3.51†
	II	5.69	3.87–7.62	0.27	II vs. III	0.40	0.91
	III	5.29	2.83–8.35	0.30	I vs. III	2.41	4.15‡
Cardiac index (L./min./sq. M.)	I	4.25	2.93–6.63	0.29	I vs. II	1.04	3.32†
	II	3.21	2.37–4.43	0.16	II vs. III	0.28	1.51
	III	2.93	1.69–4.16	0.11	I vs. III	1.72	5.10‡
Peripheral resistance (dynes sec./cm.^{5})	I	1272	687–1,599	120	I vs. II	283	1.85
	II	1555	1,113–2,290	98	II vs. III	226	1.23
	III	1781	761–3,180	132	I vs. III	509	2.52*
Central volume (Liters)	I	1.14	0.67–1.68	0.09	I vs. II	0.24	1.83
	II	0.90	0.58–2.02	0.10	II vs. III	0.02	0.16
	III	0.92	0.42–1.59	0.06	I vs. III	0.22	2.08
System volume (Liters)	I	3.51	2.20–5.94	0.27	I vs. II	0.89	3.36†
	II	2.62	2.02–3.58	0.10	II vs. III	0.24	1.04
	III§	2.86	1.59–4.62	0.18	I vs. III	0.65	2.09
Blood volume (Liters)	I	5.27	4.10–6.72	0.24	I vs. II	0.68	2.35*
	II	4.59	3.56–5.84	0.17	II vs. III	0.09	0.27
	III§	4.68	2.55–8.13	0.24	I vs. III	0.59	1.58
Blood volume (L./sq. M.)	I	2.91	2.26–3.32	0.09	I vs. II	0.31	2.42*
	II	2.60	2.16–3.43	0.08	II vs. III	0.01	0.08
	III§	2.59	1.84–4.06	0.10	I vs. III	0.32	2.02
Dye appearance time (seconds)	I	15.5	7.6–28.8	1.8	I vs. II	0.5	0.17
	II	15.0	9.3–23.2	2.1	II vs. III	4.7	1.88
	III§	19.7	6.5–35.2	1.5	I vs. III	4.2	1.71
Mean circulation time of dye (seconds)	I	28.6	16.8–50.7	2.6	I vs. II	0.0	0.00
	II	28.6	20.6–43.0	1.8	II vs. III	6.3	1.89
	III§	34.9	14.5–58.6	2.4	I vs. III	6.3	1.66
Venous pressure (mm. saline)	I	102	0–155	15.3	I vs. II	12	0.58
	II	114	35–245	13.6	II vs. III	10	0.53
	III	124	0–255	11.9	I vs. III	22	1.08

* Indicates chance probability less than 0.05.
† Indicates chance probability less than 0.01.
‡ Indicates chance probability less than 0.001.
§ Based on 24 observations instead of 25.

examination made at the time of each study. The numerical distribution in these groups is shown in table 2.

Cardiac output determinations six to 15 days after onset are hereafter designated as third studies, and those made more than 26 days after infarction are designated as fourth studies. No satisfactory separate grouping could be made which would correlate with the cardiac output and stroke

TABLE 4

Paired Analyses of Values Obtained Within 39 Hours of Onset of Acute Myocardial Infarction with Those Obtained on the Same Patients about 1 Week Later

(First and Third Determinations)

	Number of Patients	Mean Difference	Range of Difference	Ratio of Mean Difference to Its Standard Error
Stroke volume (c.c.)				
Group I	5	−6	−24, +12	0.97
Group II	5	−7	−16, −1	2.45
Group III	9	+10	−26, +27	2.06
Cardiac output (L./min.)				
Group I	5	−0.71	−2.11, +0.53	1.42
Group II	5	−0.20	−1.32, +0.60	0.59
Group III	9	−0.05	−2.47, +1.07	0.13
Peripheral resistance (dynes sec./cm.^{5})				
Group I	5	−124	−280, +128	1.65
Group II	5	−285	−569, +153	2.33
Group III	9	−152	−966, +566	0.92
All combined	19	−166	−966, +566	1.99
Central volume (Liters)				
Group I	5	−0.16	−0.44, +0.34	1.06
Group II	5	−0.07	−1.20, +0.57	0.20
Group III	9	+0.27	−0.41, +1.20	1.45
System volume (Liters)				
Group I	5	−0.46	−1.08, +0.38	1.73
Group II	5	−0.05	−1.31, +0.94	0.13
Group III	9	+0.41	−0.56, +2.09	1.70
Blood volume (Liters)				
Group I	4	+0.10	−0.85, +1.07	0.25
Group II	5	−0.45	−1.73, +0.21	1.36
Group III	8	−0.11	−0.72, +1.08	0.34

volume levels after one and four weeks of hospitalization. Therefore, observations and data collected during the third and fourth studies are reported as changes observed from the first study.

STROKE VOLUME

As will be noted in table 3, the mean stroke volume for group I was 104 c.c., for group II, 72 c.c., and for group III, 52 c.c. The difference in means

TABLE 5

Paired Analyses of Values Obtained Within 39 Hours of Onset of Acute Myocardial Infarction with Those Obtained on the Same Patients about Four Weeks Later (First and Fourth Determinations)

	Number of Patients	Mean Difference	Range of Difference	Ratio of Mean Difference to Its Standard Error
Stroke volume (c.c.)				
Group I	4	+ 3	−26, +47	0.16
Group II	5	+ 2	−22, +34	0.22
Group III	7	+34	+12, +61	5.08†
Cardiac output (L./min.)				
Group I	4	−0.23	−1.38, +1.34	0.40
Group II	5	−0.02	−1.84, +1.23	0.04
Group III	7	+1.68	+0.13, +3.08	4.18†
All combined	16	+0.67	−1.84, +3.08	1.92
Peripheral resistance (dynes sec./cm.^{5})				
Group I	4	−322	−640, + 1.5	2.32
Group II	5	−132	−735, +180	0.84
Group III	7	−575	−925, −250	2.45*
All combined	16	−373	−925, +180	4.22‡
Central volume (Liters)				
Group I	4	−0.24	−0.72, +0.46	0.96
Group II	5	−0.15	−0.50, +0.15	1.39
Group III	7	+0.08	−0.56, +0.71	0.60
Groups I and II combined	9	−0.19	−0.72, +0.46	1.50
System volume (Liters)				
Group I	3	−0.85	−1.28, −0.41	3.36
Group II	5	−0.30	−0.67, +0.09	2.11
Group III	6	+0.47	−0.08, +1.54	2.33
Groups I and II combined	8	−0.51	−1.28, +0.09	3.26*
Blood volume (Liters)				
Group I	4	+0.05	−0.63, +0.72	0.17
Group II	5	−0.52	−1.30, +0.29	1.78
Group III	7	−0.02	−0.43, +0.46	0.14
All combined	16	−0.16	−1.30, +0.72	1.16
Mean circulation time of dye (seconds)				
All combined	14	−3.1	−10.2, +2.4	2.69*
Mean blood pressure (mm. Hg)				
All combined	16	−19	−58, +16	3.44†
Venous pressure (difference between highest V. P. recorded in first 67 hours and V. P. at fourth study, in mm. saline)				
All combined	14	−43	−105, +25	4.04†

* Indicates chance probability less than 0.05.
† Indicates chance probability less than 0.01.
‡ Indicates chance probability less than 0.001.

between each group was statistically significant. The average change in stroke volume for each clinical group of patients during hospitalization is shown in tables 4 and 5. In general, there was no significant change in mean stroke volume for groups I and II during hospitalization, but the pa-

tients in group III showed a significant increase in stroke volume to equal the values observed in the other groups four weeks or more after infarction.

Cardiac Output

The mean values for cardiac output and cardiac index were highest in group I (7.70 L./min. and 4.25 L./min./sq. M.); intermediate in group II (5.69 L./min. and 3.21 L./min./sq. M.); and were lowest in group III (5.29 L./min. and 2.93 L./min./sq. M.) (table 3). The difference in means between groups I and II and between groups I and III are statistically significant (table 3). During hospitalization and treatment the observed changes in cardiac output and cardiac index were similar to those observed for stroke volume. There was no significant change in the mean values for groups I and II, whereas there was a significant increase in the mean values for group III to levels within the normal range and equal to those for groups I and II four weeks after infarction (tables 4 and 5).

Peripheral Resistance

The patients in group I with the highest mean values for stroke volume and cardiac output had the lowest mean value for peripheral resistance (1,272 dynes sec./cm.^{5}); group II was intermediate with a mean of 1,555 dynes sec./cm.^{5}; and group III had the highest mean peripheral resistance (1,781 dynes sec./cm.^{5}) (table 3). The difference in mean peripheral resistance between groups I and III is probably significant (chance probability, less than .02).

Sixteen patients were studied again four weeks or more after admission, and there was a significant decrease in total peripheral resistance when compared with the initial studies. The average decrease amounted to 373 dynes sec./cm.^{5} (p less than 0.001). There was also a significant drop in mean blood pressure (average = 19 mm. Hg) over the same period in these patients (p less than 0.01) (table 5).

Interrelationship of Blood Pressure, Stroke Volume and Peripheral Resistance

A significant inverse correlation between stroke volume and total peripheral resistance was observed in the 54 determinations performed within 67 hours of the clinical onset of the infarction. The coefficient of correlation was — 0.61, with a chance probability less than 0.001.

The data regarding blood pressure, stroke volume and peripheral resistance for the 17 patients who were studied twice within 67 hours after onset of their infarction are presented in table 6. A marked fall in blood pressure following an acute myocardial infarction certainly does not always imply that a marked drop in stroke volume has occurred. The only two patients with a significant rise in stroke volume (15, 18 c.c.) from the first

to the second study had a marked drop in blood pressure and peripheral resistance (— 593, — 372 dynes sec./cm.^{5}). The patient with the greatest decrease in peripheral resistance (— 880 dynes sec./cm.^{5}) showed a marked fall in blood pressure while maintaining approximately the same stroke volume (62 and 64 c.c.), and the second determination of peripheral resistance in this patient, 1,099 dynes sec./cm.^{5}, was still within the normal range. The two patients with the lowest stroke volume initially (45 and 30 c.c.) were both hypertensive and showed a marked decrease in blood pressure and peripheral resistance (— 630 and — 700 dynes sec./cm.^{5}) between the two determinations, with a fall in stroke volume of only 7 and

TABLE 6

Tabulation of Blood Pressure, Stroke Volume and Peripheral Resistance Data for 17 Patients with Two Studies Within 67 Hours Following Acute Myocardial Infarction

Patient		First Study			Second Study			Change from 1st to 2nd	
No.	Name	B. P.*	Stroke Volume (c.c.)	Periph. Resist.†	B. P.*	Stroke Volume (c.c.)	Periph. Resist.†	Stroke Volume (c.c.)	Periph. Resist.†
5	S. M.	112/65	100	888	104/62	73	1,140	−27	+252
9	F. H.	60/50	63	761	84/66	62	972	− 1	+211
10	S. R.	120/80	69	1,216	112/98	60	1,317	− 9	+101
13	A. C.	170/80	86	2,080	168/72	70	2,290	−16	+210
20	V. B.	210/130	65	1,752	190/143	54	2,479	−11	+727
26	N. F.	130/96	65	1,198	105/70	61	1,280	− 4	+ 82
30	A. H.	110/60	51	1,677	128/70	51	1,770	0	+ 93
39	H. M.	130/88	75	1,142	110/84	54	1,218	−21	+ 76
14	W. H.	215/140	64	1,985	165/108	79	1,392	+15	−593
17	M. K.	220/125	45	2,960	155/110	38	2,330	− 7	−630
21	J. P.	135/105	70	1,196	125/95	54	1,157	−16	− 39
24	P. F.	152/106	98	1,505	129/90	116	1,133	+18	−372
29	B. D.	192/108	74	2,378	120/90	44	2,273	−30	−105
34	F. G.	98/74	81	1,180	96/72	79	1,113	− 2	− 67
38	L. R.	142/96	62	1,979	97/67	64	1,099	+ 2	−880
41	A. M.	150/110	30	3,180	106/70	28	2,483	− 2	−700
44	G. B.	155/85	94	1,599	108/70	90	1,310	− 4	−289

* B. P. = Blood pressure, systolic/diastolic, mm. Hg.
† Peripheral resistance in dynes seconds/cm.^{5}

2 c.c. Nevertheless, the peripheral resistance in both cases remained elevated (2,330 and 2,483 dynes sec./cm.^{5}). The patient with the greatest decrease in stroke volume (from 74 to 44 c.c.) was also hypertensive, and he had a marked drop in blood pressure with relatively little decrease in his abnormally high value for peripheral resistance (from 2,378 to 2,273 dynes sec./cm.^{5}). The values for peripheral resistance were within the normal range in the other three patients who showed a decrease in resistance at the time of the second study, and the stroke volume was 54, 79 and 90 c.c., which represented a decrease of 16, 2 and 4 c.c., respectively.

Two of the eight patients who had an increase in peripheral resistance

developed an abnormally elevated value (2,290 and 2,479 dynes sec./cm.^{5}), with a decrease in stroke volume of 11 and 16 c.c. and only a slight change in blood pressure. The other six patients who had an increase in peripheral resistance showed an average decrease in stroke volume of 10 c.c. below their initial level. The patient who had the lowest value for peripheral resistance, 761 dynes sec./cm.^{5}, is discussed in greater detail in a later section.

Venous Pressure

The average venous pressure for each group was lowest in group I (102 mm. saline), intermediate in group II (114 mm. saline), and highest in group III (124 mm. saline). However, because of the wide range of values within each group, there was no statistically significant difference between any of these (table 3). The venous pressure was measured again four weeks or more later in 14 patients, and there was an average decrease of 43 mm. saline from the highest value that had been obtained within 67 hours following onset of infarction (table 5).

Circulation Times

A wide range of values (12 to 60 seconds) was observed for the Decholin circulation time in 27 patients studied within 39 hours after onset of the infarction, and the mean value was 22.7 seconds (standard error of mean = 1.8 seconds). This determination of arm-to-tongue circulation time was discontinued as a routine procedure because of the high incidence of nausea and vomiting which it precipitated in those patients studied within three days of the onset of their infarction. There was no significant difference in means between the three clinical groups for the dye appearance time or for the mean circulation time. The average values for the dye appearance time for clinical groups I and II were almost the same (15.5 and 15.0 seconds), whereas a longer time (19.7 seconds) was obtained for group III. A similar relationship between the clinical groups was observed for the mean circulation times, i.e., identical average values for groups I and II (28.6 seconds), and a longer average time (34.9 seconds) for group III (table 3). When the mean circulation time was determined again four weeks or more later in 14 patients, an average decrease of 3.1 seconds had occurred (table 5).

Central Volume and System Volume

In an effort to determine the actively circulating intrathoracic blood volume and the amount contained in the lungs, different investigators [8, 11, 12] have made various modifications in the technic of the dye injection and in the analysis of the data. Newman and associates [8] have proposed the calculation of a "central volume," which represents the largest volume in which the dye is distributed at any instant during its first circulation. In this series of

patients the average central volume for groups I, II and III was 1.14, 0.90 and 0.92 L., respectively, and there was no significant difference between the three clinical groups (table 3). For the 10 patients who did not change clinical groups there was an average increase in central volume of 0.26 L. from the first to the second study (standard error mean difference = 0.09 with p less than 0.02). Otherwise, there were no consistent or significant changes in the mean value for any group, or for all patients combined during the hospitalization (tables 4 and 5).

Another technic employed to estimate intrathoracic blood volume has been to multiply the cardiac output by the mean circulation time of dye between the venous injection site and the collection point in a peripheral artery.[12] Since there is a definite extrathoracic component to this calculated volume, we shall hereafter refer to it as system volume. Freis et al.[1] injected the dye through a catheter into a more central vein and reported similar measurements as central volume. Since the values and the methods of calculation are very different from the central volume of Newman, previously described, this difference in terminology must be kept in mind.

There was a significant difference between the mean system volume of group I (3.51 L.) and group II (2.62 L.). The mean system volume for group III (2.86 L.) was intermediate in value and was not statistically different from the mean value for either of the first two groups (table 3).

The eight patients in groups I and II on admission who were studied again four weeks or more later showed a combined average decrease in system volume of 0.51 L. over this period. The patients in group III had an increase in average system volume during this period, but this was not significant (table 5).

Blood Volume

The average blood volume was greatest in group I (2.91 L./sq. M. body surface area), and in groups II and III the average was about 10% less (2.60 and 2.59 L./sq. M., respectively) (table 3). The only possible significant difference in average blood volume between the clinical groups was between group I and group II (p less than 0.05). Within group III the range of values was so great as to make the difference from group I not statistically significant. Both the lowest values (1.84 L./sq. M.) and the highest (4.06 L./sq. M.) obtained for blood volume were in group III patients. It was recognized that the criteria used for the grouping of these patients considered chiefly those observations reflecting the adequacy of the left ventricle, and that other factors, such as venous pressure, size of the liver, etc., might show more correlation with the measurements of the blood volume. Therefore, all of the observations on plasma volume and blood volume obtained within 67 hours of the onset of infarction were reviewed, along with venous pressure measurements, and there appeared to be no definite correlations. Likewise, there appeared to be no correlation between changes from

TABLE 7
Summary of Hospital Course

		Recovered				Died		
			Specific Cardiac Therapy					
		Uneventful Course	Quinidine or Pronestyl for PVC's	Digitalis for Cardiac Failure	Quinidine and Digitalis	Probable Ventricular Fibrillation	Acute Cardiac Failure	Congestive Heart Failure
Cardiovascular History Prior to Admission	Angina without infarction	4	0	0	1	0	0	0
	Previous acute infarction	2	0	1	1	2	0	0
	Hypertension	2	2	0	0	0	1	0
	Hypertension and angina	1	1	1	0	0	0	0
	Hypertension and infarction	1	1	0	0	0	0	0
	Digitalis and angina	0	1	—	—	0	0	0
	Digitalis and infarction	0	0	—	—	0	2	0
	Digitalis and hypertension	0	0	—	—	0	0	1
	Negative	8	2	1	1	1	1	0
Classification on First Study	Group I	8	1	0	0	2	0	0
	Group II	4	4	1	2	1	0	0
	Group III	6	1	2	1	0	4	0
	Delayed hospitalization	0	1	0	0	0	0	1
Total for 39 patients		18	7	3	3	3	4	1

the first to the second study in these measurements. There was no consistent change in the average blood volume for these patients or for any of the clinical groups during the hospitalization (tables 4 and 5).

HOSPITAL COURSE

The hospital course of these patients is briefly summarized in table 7. In the upper part of the table the patients have been grouped according to their cardiovascular history prior to the present acute myocardial infarction. In the lower part of the table the same data are presented to show the sub-

sequent outcome for the patients who were classified in the various clinical groups at the time of the first cardiac output determination. Thirty-one patients recovered from their illness and were discharged from the hospital. Eighteen patients had an uneventful hospital course and responded to the usual therapy of bed-rest, oxygen, anticoagulants, analgesics and sedatives as needed. Seven patients developed a significant number of premature ventricular contractions, which were controlled with antifibrillatory drugs, notably quinidine sulfate, with the exception of one patient who was given procaine amide hydrochloride (Pronestyl). Three patients developed signs of moderately severe cardiac failure while at bed-rest and were given digitalis preparations, with good response. Three additional patients required both digitalis and quinidine for the above reasons.

The three deaths listed as probably due to ventricular fibrillation occurred in group I and II patients, two of whom had a history of previous myocardial infarction. These deaths happened suddenly during the first 19 hours of hospitalization in male patients whose course until then had appeared to be satisfactory, with good blood pressure and without appreciable evidence of cardiac failure. Ventricular fibrillation was confirmed by electrocardiogram immediately prior to death in only one of these patients, and a postmortem examination in another revealed no indication of other cause of death. Six of the 11 patients in group II who recovered developed sufficiently frequent premature ventricular contractions to require treatment with quinidine or Pronestyl, whereas only two of the 10 patients in group III who recovered required antifibrillatory drugs.

The four deaths due to acute cardiac failure occurred in group III male patients. Two normotensive patients, 62 and 76 years of age, who had been on maintenance digitalis therapy following a previous myocardial infarction, died in a shocklike state with pulmonary edema on the first and fourth hospital days, respectively. One 40 year old patient with known hypertension but without previous infarction or digitalis therapy was digitalized 24 hours after admission because of progressively severe cardiac failure but died 22 hours later. Another patient, 55 years of age, without previous cardiovascular disease, was digitalized on the second hospital day because of acute cardiac failure which persisted and caused his death on the sixth hospital day. The other patient who died was a 69 year old male with known hypertension who had been digitalized five months previously and who was admitted to the hospital five days after the onset of his acute infarction. He developed angina decubitus and progressive congestive heart failure and died in pulmonary edema on the thirty-fifth hospital day.

Shock Following Acute Myocardial Infarction

Two patients presented the typical clinical appearance of a shocklike state, with blood pressures of 95/85 and 90/80 mm. of Hg at the time of cardiac

output determination, and they had values for peripheral resistance of 1,432 and 2,367 dynes sec./cm.^{5}, with stroke volume of 43 and 22 c.c., respectively.

A significant hypotension, which may often be confused with a true state of shock, may develop because of cardiac arrhythmias, with resultant displacement of blood from the arterial to the venous side and to the pulmonary vessels.[13] One patient in this series entered the hospital with rapid auricular fibrillation (ventricular rate, 178 per minute) and the clinical appearance of shock, with a blood pressure of 40/0 mm. Hg. He was given 1.2 mg. digitoxin intravenously, and at the time of cardiac output determination, four hours later, he had a regular sinus rhythm at 96 per minute and presented none of the signs or symptoms of shock except for a blood pressure of 60/50 mm. Hg. The following values were obtained at this study: stroke volume of 63 c.c., cardiac index of 3.03 L./min./sq. M., and total peripheral resistance of 761 dynes sec./cm.^{5} Only these three patients had a pulse pressure as small as 10 mm. Hg at the time of study, and the latter patient with the abnormally low value for peripheral resistance was the only one who survived his illness and was discharged from the hospital.

Discussion

Control Studies: No control patients are included in this report. Valid control subjects, ideally, should be without any cardiopulmonary disease, in the same age group and predominantly male, who were admitted to the hospital with a painful disorder for which they had received similar analgesics and sedatives prior to study. For this reason we have chosen to include only patients with acute myocardial infarction and to analyze the differences in values obtained within this group. Prior to these studies we performed approximately 30 cardiac output determinations in patients with various diseases to establish a standard procedure.

Grouping of Patients: In the selection of criteria for grouping these patients, great emphasis has been placed on blood pressure measurements and the changes therein, and on the clinical evidence of pulmonary congestion. These factors, which are frequently thought of as varying directly with the adequacy of the left ventricle, together with the heart rate and rhythm, were the measurements that we found to vary most systematically with the cardiac output and the stroke volume in these patients with acute myocardial infarction. Other observations, such as heart size and liver size as determined by physical examination, and venous pressure determinations, although of value in forming the clinical picture, showed wide variations with regard to the level of the cardiac output and stroke volume. Likewise, the history, symptoms and, to a great extent, the physical appearance, and electrocardiographic findings on admission could not be used to distinguish which patients would have the lowest cardiac output and stroke volume. Patients whose hospitalization is delayed beyond 20 hours after the clinical onset of infarction will in many cases already have sustained

a considerable drop in blood pressure. Therefore, any attempt to classify these patients according to our criteria might be misleading.

Stroke Volume and Cardiac Output: The cardiac output and cardiac index in the great majority of these patients were within the range of values commonly accepted as normal for patients in the basal state. All patients were resting quietly and had been given opiates and sedatives whenever needed to make them as comfortable as possible. However, there was no attempt at obtaining the basal state prior to study, since we were primarily interested in performing the measurements at the earliest time after the infarction.

Gross, Mendlowitz and Schauer [14, 15] performed ligation of a coronary artery in a series of dogs and found the cardiac output 24 hours later to be equal to or greater than that observed prior to ligation. Orias [16] in 1932 demonstrated that immediately after ligation of the anterior descending coronary artery in dogs there was a fall in stroke volume, aortic pressure and pulse pressure, but within 4 to 7 minutes these measurements were equal to or greater than those that had existed prior to ligation in 20 of the 23 experiments. In the three experiments in which recovery did not occur there was progressive dilation of the heart, with rapidly developing failure and death.

In contrast to the prompt recovery from the decreased stroke volume observed following experimental ligation of a coronary artery, many of the patients (group III) in this study showed a distinctly lowered stroke volume. In these patients the myocardial fibers outside the area of acute infarction probably were not able to maintain stroke volume because of previous injury and strain from hypertension or coronary arterial disease, or else the area of acute infarction was so large that relatively few fibers of the left ventricle escaped injury. It seems reasonable to postulate that with the onset of acute myocardial infarction in patients, as in experimental animals, there is primarily a fall in stroke volume, and if the uninjured muscle fibers are not able to respond adequately to the increased diastolic filling and to overcome the burden imposed by the poorly contractile injured fibers and by the further loss of energy in the paradoxic movement of the infarcted muscle wall, then the stroke volume remains lowered.[13, 17]

Peripheral Resistance: The significant inverse correlation between stroke volume and peripheral resistance, that was observed acutely, is most probably an example of the reflex increase in total peripheral resistance that occurs when there is a fall in arterial blood pressure.[10, 17] In these patients the latter would be secondary to a decreased stroke volume and cardiac output.

Nine of the 17 patients who were studied twice within 67 hours of the onset of their infarction had a decrease in peripheral resistance between the two determinations. An increase in stroke volume and cardiac output occurred in only three of these nine patients, but this was not great enough to prevent a fall in their mean blood pressure of 19 mm. Hg or more.

Even though there was no significant rise in stroke volume and cardiac output for the 16 patients as a group who were studied four weeks or more after hospitalization, there was a significant decrease in peripheral resistance and mean blood pressure during this time. Whether this was due directly to the infarction or to the four weeks of bed-rest cannot be determined from these data. This decrease in peripheral resistance following an acute myocardial infarction would appear to be physiologically desirable in those patients with a failing heart and would result in an increased stroke volume with a reduction of diastolic size of the heart, provided the head of pressure at the coronary ostia did not fall below the normal range and there was no further decrease in the perfusion of blood through the coronary arteries.[18, 19]

Venous Pressure: The significant decrease in venous pressure during the four weeks of hospitalization is evidence that there was cardiac failure on admission, even though the average cardiac output was not significantly below the normal range.

Circulation Time: The arm-to-tongue circulation time in practically all determinations was greater than the dye appearance time and less than the mean circulation time of the dye. Fishberg, Hitzig and King [20] reported a similarly wide range of values for the arm-to-tongue circulation time in patients with acute myocardial infarction, and Selzer [21] found an average value of 24.3 seconds in a study of 45 patients.

System Volume: The lack of significant difference between the system volume of group III and either of the other groups suggests that the lowered cardiac output and stroke volumes observed in group III were due to myocardial failure rather than to a decreased venous return to the heart. This is in agreement with the findings of Freis et al.[1] Hamilton and associates in 1932 [6] found a direct correlation between stroke volume and system volume in both men and dogs with normal hearts. When cardiac decompensation occurred a direct correlation was observed again, but for the same system volume, the stroke volume was much smaller than was observed during the compensated state. Thus, the decrease in system volume in the group I and II patients after four weeks of hospitalization in the absence of any significant change in stroke volume and cardiac output is further evidence that cardiac failure was present initially in these patients. Since the group III patients had a significant increase in cardiac output during this period, the lack of significant change in system volume for them does not nullify this conclusion.

Blood Volume: A slightly lower blood volume in some patients following acute myocardial infarction has also been reported by others.[22, 23] Stead and Ebert [24] have suggested that transudation of fluid in the lungs might explain the reduction in blood volume. The profuse diaphoresis, vomiting and reduced fluid intake are other factors to be considered. A generalized increase in venous pressure following an acute myocardial infarction could

cause an increased filtration of fluid from the capillaries into the extracellular space, resulting in a decreased plasma volume. The factors which limit the possible decrease in plasma volume by this means have been discussed by Landis and Hortenstine.[25]

Shock Following Acute Myocardial Infarction: Whether the shocklike state sometimes seen following an acute myocardial infarction is due to a failure of peripheral vasomotor mechanisms or is due primarily to myocardial failure has been a controversial subject for several years.[13, 20, 23, 24] The quantitative analysis of the dye dilution curve in these patients is sometimes impossible. However, in the two patients in this series in which this could be done, and in four determinations performed in three such patients by Freis, Schnaper, Johnson and Schreiner,[1] there was no evidence of peripheral vascular collapse, and in most instances the calculated value for peripheral resistance was above normal. The one patient in our series who had an abnormally low peripheral resistance and a pulse pressure as small as 10 mm. Hg at the time of study had none of the signs or symptoms of shock except for a blood pressure of 60/50 mm. Hg.

Summary

1. A total of 96 determinations of cardiac output were performed in 39 patients with acute myocardial infarction using the dye dilution technic. Fifty-four determinations were made in 37 patients within 67 hours of the clinical onset of the infarction. The various measurements from each of the studies performed within 67 hours of onset of the infarction were placed in one of three groups, depending upon the clinical condition of the patient at the time of study, and using the criteria of blood pressure, heart rate and rhythm, and pulmonary congestion.

2. The differences observed in mean values for stroke volume, cardiac output, peripheral resistance, venous pressure, circulation time, central volume, system volume and blood volume between the different groups and in the various groups during hospitalization are presented.

3. Many of the patients who were hospitalized, placed at bed-rest and treated soon after the onset of an acute myocardial infarction were able to maintain their circulation of blood at levels equal to those seen in normal persons in the basal state. This was true even for several of the patients in group III who had sustained an appreciable drop in mean blood pressure or pulse pressure. Those patients who had very low levels of cardiac output and stroke volume initially and who were able to survive their illness showed an increase in cardiac output and stroke volume when studied approximately four weeks later.

4. A significant decrease in mean blood pressure, total peripheral resistance and venous pressure was observed in the patients studied again after four weeks of hospitalization.

5. Changes observed in venous pressure, mean circulation time and system volume during hospitalization indicate that cardiac failure was present at the time of the initial study, even though the cardiac output was not significantly reduced.

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SUMMARIO IN INTERLINGUA

1. In 39 patientes con acute infarcimento myocardiac, 94 determinationes de rendimento cardiac esseva executate per medio del technica a dilution de colorante. Cinquanta-quatro de iste determinationes esseva executate in 37 patientes intra 67 horas post le declaration clinic del infarcimento. Le condition clinic de iste 37 patientes al tempore del studio esseva evalutate super le base de pression sanguinee, frequentia e rhythmo cardiac, e congestion pulmonar e tunc usate como criterio in arrangiar le varie datos obtenite in tres gruppos.

2. Es presentate le differentias que esseva observate durante le hospitalisation inter e intra le varie gruppos in le valores median de volumine per pulso, rendimento cardiac, resistentia peripheric, pression venose, tempore circulatori, volumine central, volumine systemic, e volumine de sanguine.

3. Multes del patientes hospitalisate, allectate, e tractate promptemente post le declaration de un acute infarcimento myocardiac manteneva lor circulation de sanguine a nivellos equal a illos observate in personas normal in le stato basal. Isto esseva ver mesmo in le caso de plure patientes in Gruppo III qui habeva suffrite un appreciabile reduction del valores median del pression sanguinee o del pression del pulso. Ille patientes qui habeva basse nivellos initial del rendimento cardiac e del volumine per pulso monstrava—in tanto que illes superviveva—un augmento del rendimento cardiac e del volumine per pulso quando illes esseva examinate circa quatro septimanas plus tarde.

4. In le patientes restudiate quatro septimanas post lor hospitalisation un significative reduction esseva constatate in le valores median del pression sanguinee, del resistentia peripheric total, e del pression venose.

5. Cambiamentos durante le hospitalisation in le pression venose, le tempore median de circulation, e le volumine systemic indica que dysfunctionamento cardiac esseva presente al tempore del studio initial, mesmo si le rendimento cardiac non esseva significativemente reducite.

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ANEURYSMAL DILATATION OF AORTIC SINUSES IN ARACHNODACTYLY: DIAGNOSIS DURING LIFE IN THREE CASES *

By Israel Steinberg, M.D., F.A.C.P., and William Geller, M.D.,
New York, N. Y.

Arachnodactyly (Marfan's syndrome) is a rare hereditary disease of unknown etiology. It is characterized by widespread malformations of the skeletal, cardiovascular and ophthalmic systems. Marfan in 1896 [1] described the first case and called attention to the long, thin, spider-like appearance of the extended extremities. Soon arachnodactyly [2] became established as the name of the disorder.

The association of cardiovascular anomalies with arachnodactyly became evident with complete autopsies. Forty-one necropsies of Marfan's disease have been reported; eight were under 28 months of age and had no aortic lesions; the remaining 33 were adults (14 to 55 years); all had lesions of the great vessels. Baer, Taussig and Oppenheimer [3] were the first to call attention to the characteristic cardiovascular involvement: medial degeneration of the aorta producing aneurysmal dilatation of the ascending aorta, endocardial valvular thickening, and marked cardiac hypertrophy. Reports of sudden death due to rupture of dissecting aneurysms then followed,[4-13] and by January, 1955, the sixteenth necropsy finding of aortic dissection in this disease was reported.[7, 11-13] In addition, a case of medial degeneration with aneurysmal dilatation and incomplete rupture of the pulmonary artery [15] in Marfan's disease was also reported, whereas previously only questionable medial degeneration [3] and pulmonary artery aneurysm [16] were recorded.

Aneurysmal dilatation of the aortic sinuses of Valsalva in a case of arachnodactyly was found twice at necropsy.[10, 17] The purpose of this report is to describe aneurysmal dilatation of the aortic sinuses in three living patients. Diagnosis was made by angiocardiography.

Case Reports

Case 1. A 40 year old white male librarian was seen in January, 1954, because of increasing enlargement of the heart. The first knowledge of heart trouble was at the age of 16 years, when a heart murmur was heard during a routine physical examination. Ten years later he consulted a cardiologist because of tachycardia and "extra beats," and a diagnosis of rheumatic heart disease with mitral stenosis and insufficiency was made. In the last six years, yearly chest x-rays had shown an in-

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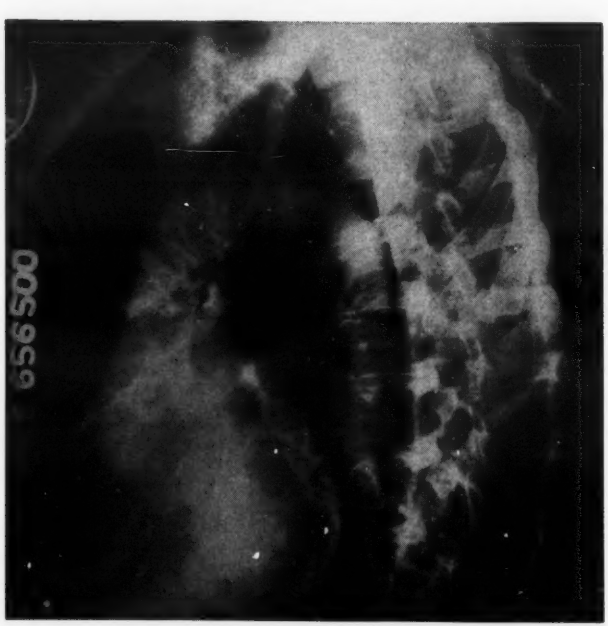
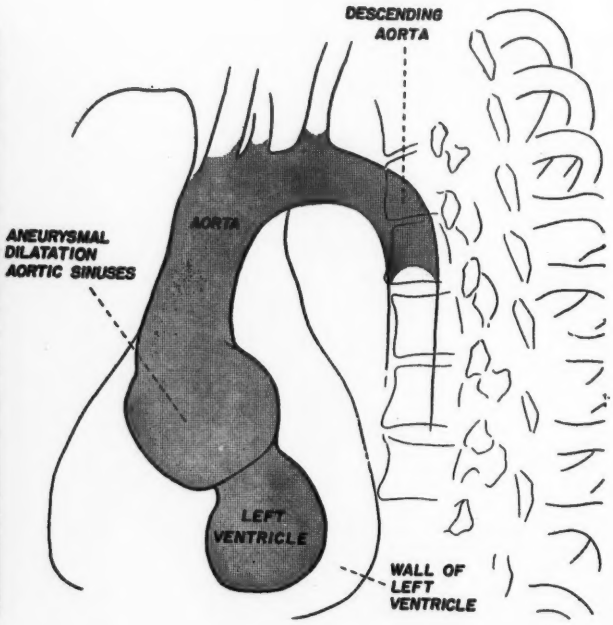
A B

FIG. 1. *Case 1. A.* Frontal teleroentgenogram shows enlargement of the heart, especially the left ventricle. *B.* Left anterior oblique view also reveals the left ventricular enlargement.





A B

FIG. 2. *Case 1. A.* Angiocardiogram, left oblique view, demonstrates aneurysmal dilation of the aortic sinuses. The left ventricular wall is hypertrophied. *B.* Tracing of *A.*

crease in size of the heart. However, the patient denied dyspnea, chest pain, edema or limitation in ability to work.

The patient recalled no serious illnesses in the past. He denied chorea, sore throats, rheumatism or muscle pains. At the age of nine years, dislocation of the right lens was noted. Right iridectomy was done at age 22, and a year ago (at 39) he had a left iridectomy. Rapid skeletal growth occurred during adolescence, with the appearance of long thin bones and tapering fingers. A slight limp of the right leg developed at that time. The patient remembered a great uncle with similar physique. There are two children: a daughter, who is free of the stigmata of the disease, and a son, age 5 who has arachnodactyly.

Physical examination revealed a lanky, thin man wearing thick lensed glasses; height, 6 feet 2 inches; weight, 168 pounds. The skull was dolichocephalic. The fingers were long, gracile and tapering. The right lower extremity was one inch shorter than the left. Eye examination revealed bilateral iridectomy scars. The ears were long and large, and the palate was high and arched. The scapulae were prominent. The chest cage was long and thin, and there was bulging of the right upper anterior thorax. Examination of the lungs was normal.

Heart examination revealed a blood pressure of 130/70 mm. of Hg; the pulse was 56 per minute; the rhythm was normal sinus, with an occasional premature contraction. Forcible cardiac contractions were seen over the left anterior thorax. The heart was enlarged, the position of maximal impulse and the left border of dullness being in the left anterior axillary line in the fifth left interspace. A loud systolic murmur with maximal intensity over the apex was transmitted widely to the left axilla and back, and along the right sternal border. The first sound at the apex was loud, and the heart sounds were distant over the base of the heart. Electrocardiographic study revealed no abnormalities.

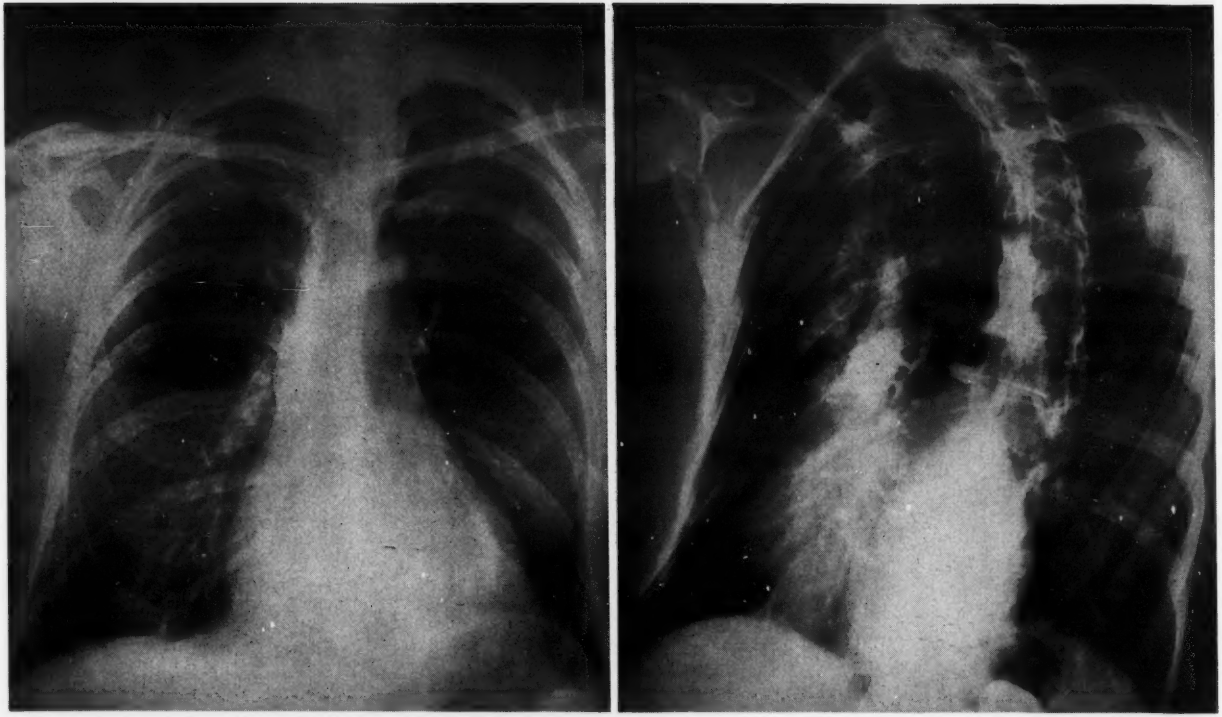
Roentgenographic examination of the heart (figure 1) revealed enlargement, especially of the left ventricle. The lungs were clear. Angiocardiography on May 6 in frontal and left oblique views showed an enlarged left ventricle and aneurysmal dilatation of the aortic sinuses (figure 2).

Case 2. A 47 year old white woman was admitted on December 6, 1954, because of sudden onset of severe right chest pain. This had first occurred on August 8 during light housework and lasted for a short time. The next attack was also brief and occurred two weeks prior to entry, but it was more severe and of a "tearing" character, with intense pain across the chest radiating through to the back and toward the right side of the thorax. The only other complaints were increasing weakness and dyspnea on mild exertion of three months' duration. Chest x-rays had been taken in 1936, 1938 and 1948, when the patient was observed for fibrocystic masses in the breasts. No heart enlargement had been seen, and there were no cardiac murmurs.

In the past the patient had been in good health, and it was only in recent years that she noted aches in the knees, hips and low back. At age seven years, severe myopia was discovered and glasses were prescribed. The patient was unmarried; an only sister and an 85 year old mother were both free of the stigmata of arachnodactyly. Of interest is the patient's statement that strangers mistake her for her mother.

On examination the patient was tall and thin; height, 5 feet and 10 inches; weight, 166 pounds. She wore thick lensed glasses, and the dolichocephalic skull with long ears, beaked nose and small lower jaw gave a characteristically wise and prematurely old appearance. The eyes were deep-set and severely myopic. The palate was high and arched. The sternum bulged and was ridged, and there were kyphosis and scoliosis of the dorsal spine. The fingers were unusually long and could easily be hyperflexed; the feet, too, were unusually long and narrow.

The heart was enlarged beyond the anterior axillary line, and there were a heaving, forcible apical thrust and a presystolic thrill. Also at the apex a rough, rumbling,



A B

FIG. 3. *Case 2. A.* Frontal teleroentgenogram shows cardiac enlargement and scoliosis of the spine. *B.* Left anterior oblique film also shows the left ventricular enlargement.

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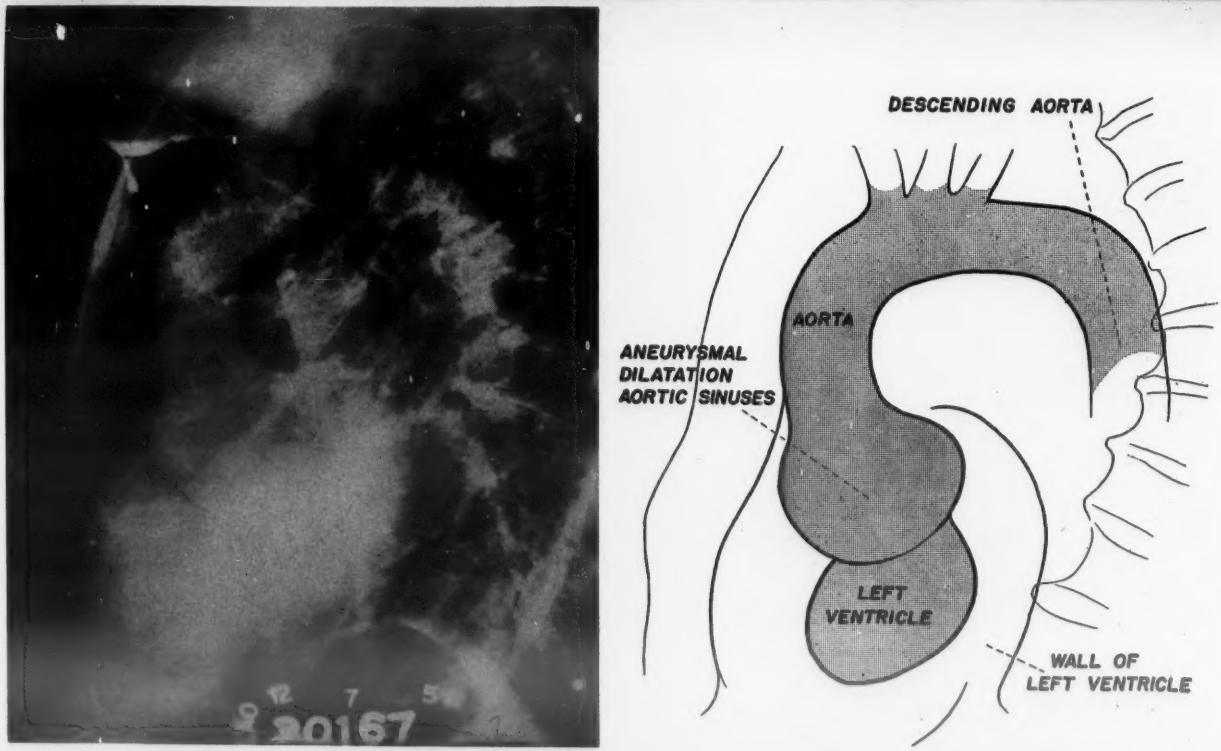

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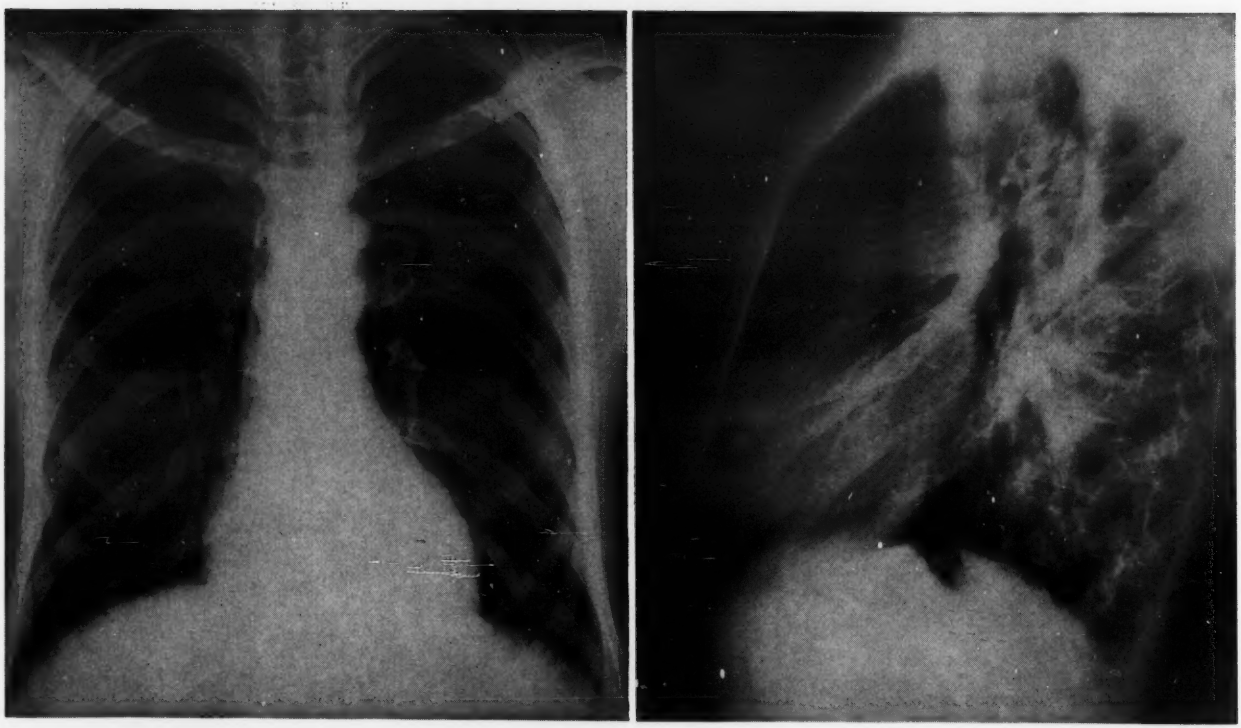
FIG. 4. *Case 2. A.* Angiocardiogram, left anterior oblique view, reveals aneurysmal dilatation of the aortic sinuses of Valsalva and left ventricular enlargement. The aorta is tortuous and unfolded. *B.* Tracing of *A.*

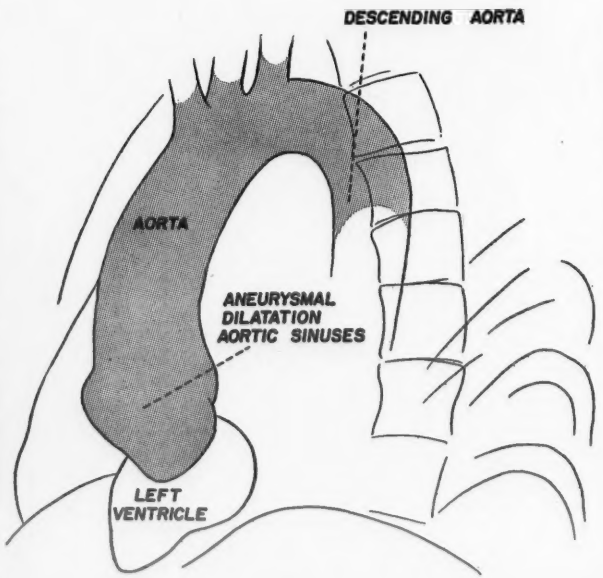


A B

FIG. 5. *Case 3. A.* Frontal chest film shows a normal heart silhouette. *B.* Left anterior oblique view is also normal.

A B

FIG. 5. *Case 3.* *A.* Frontal chest film shows a normal heart silhouette. *B.* Left anterior oblique view is also normal.



A B

FIG. 6. *Case 3.* *A.* Angiocardiogram, left anterior oblique projection, shows aneurysmal dilatation of the aortic sinuses. *B.* Tracing of *A.*

grade IV presystolic murmur was heard, while at the aortic area there was a high-pitched, blowing diastolic murmur radiating along the left sternum to the apex. The pulses were full, bounding and regular. The blood pressure was 140/60 mm. of Hg, right arm; 150/70 mm. of Hg, left arm. The lungs were clear, the liver was enlarged but nontender, and there was no edema of the extremities.

The electrocardiogram demonstrated deviation of the electrical axis to the left and left ventricular hypertrophy. The chest roentgenograms (figure 3) showed scoliosis of the thoracic spine, bulging of the sternum (figure 3B) and cardiac enlargement, especially of the left ventricle. Fluoroscopy disclosed unusually active pulsations at the root of the aorta. Angiocardiography on December 7 in the frontal and left oblique positions disclosed aneurysmal dilatation of the aortic sinuses, left ventricular enlargement and arteriosclerotic tortuosity and unfolding of the aorta (figure 4).

Soon after admission the patient improved and became asymptomatic. At entry the venous pressure was elevated (160 mm. water), and the circulation time (Decholin) was prolonged. Accordingly, digitalis was prescribed and after a week the patient was discharged.

Case 3. A 23 year old college student was first seen in 1948, at age 16 years, because of chronic constipation. The long, thin habitus, with unduly elongated tapering fingers and toes, readily suggested arachnodactyly. In spite of his height (6 feet 1¾ inches), he weighed only 134 pounds. In addition, he was myopic and wore glasses. His head was flattened from side to side; the ears were long; the palate was high and arched, and the ribs and scapulae were prominent. Examination was normal except for a soft apical systolic murmur; the blood pressure was 110/80 mm. of Hg. Roentgen examination showed no cardiac enlargement; the long bones were unduly elongated, and barium enema studies showed a congenital megacolon. Although all other members of the family were tall, none showed the stigmata of Marfan's syndrome.

On recent reëxamination the patient was entirely asymptomatic. His weight was 156 pounds; height, 6 feet 4½ inches. Examination of the heart showed the rate to be 80, regular sinus rhythm; blood pressure, 120/60 mm. of Hg. Forcible contractions of the heart were visible over the precordium, the point of maximal pulsation being 10 cm. from the mid sternum in the fifth left intercostal interspace. An apical systolic thrill was felt, and a loud (grade III) systolic murmur, loudest at the apex, was heard all over the precordium and posterior part of the chest. The second sound at the apex was split.

Electrocardiographic studies revealed sinus arrhythmia and partial incomplete heart block (QRS, 0.11 sec.). Roentgen examination of the heart was normal (figure 5). Angiocardiographic studies on January 11, 1955, demonstrated aneurysmal dilatation of the aortic sinuses (figure 6).

Discussion

The cause of arachnodactyly is unknown. A recent attractive theory [14] (which will, however, have to await histologic examination of the ligamentous attachments and long bone epiphyses) is that the disease is due to abnormalities of the endocrine system causing disturbance of ground substance. This concept supposes that lesions similar to the medial degeneration of the aorta occur in ligamental and bone tissues. The recent experimental production of kyphoscoliosis, periosteal new-bone formation and dissecting aneurysms of the aorta in rats fed diets containing 50% sweet pea seeds is believed to be due to defective formation or excessive destruction

of the chondroitin sulfate of the ground substance.[18] This suggests that arachnodactyly may be due to a hereditary defect in chondroitin sulfate metabolism.

Our patients had many of the characteristic clinical features of arachnodactyly, which often permit diagnosis at a glance. All were tall, slender and lanky, with dangling, thin, spider-like limbs. The skulls were dolichocephalic. The ears were long and large, and the long, thin faces, topped by heavy thick glasses gave them a wise and prematurely old appearance. The palates were arched and high. One leg was shorter than its mate and caused limping in case 1. Skeletal deformities are due to poorly developed and relaxed ligaments and muscles, which cause spinal and thoracic malformations such as scoliosis, kyphosis, and funnel and pigeon breast.

Ocular abnormalities are also common, occurring in up to 75% of cases. Congenital bilateral dislocations of the lens due to poor ligamentous support and myopia cause serious progressive deterioration in vision. For these reasons, arachnodactyly is well known and appears frequently in the ophthalmologic literature.[19]

Over 350 cases of arachnodactyly have been reported. The incidence of cardiovascular involvement is uncertain, but is estimated as being 30 to 60%. A review in 1953 of 34 autopsied cases with cardiovascular lesions revealed that aortic lesions were present in 22 cases.[12] Of these, dissecting aneurysm accounted for 12; fusiform aneurysm, seven; and a dilated aortic ring, three. Endocardial lesions were present in 21 instances, mostly valvular (only two were mural). The mitral and aortic valves were involved in five and 10 instances, respectively. Combined aortic and endocardial lesions occurred 13 times. Congenital septal defects were present in eight cases; four of these also had aortic aneurysms and, contrary to earlier reports, septal defects were less common than the occurrence of disease in the aorta. Further reports of autopsied cases bring the total to 41.[11, 13-16]

Aortic aneurysms in arachnodactyly have varied in size, shape and location. They often begin just distal to the aortic valve and are usually fusiform. Many end at the innominate artery, while some extend to the left subclavian artery or abdominal aorta. Three were also associated with coarctation of the aorta.[6, 8, 11] Although there may be variations in the gross appearance of the aortic aneurysms, the microscopic picture is constant and consists of degeneration of the elastic and muscle fibers in the media and replacement by loose, collagenous fibrous tissues.[5, 9, 12] However, the medial aortic degeneration has no specific histologic features and is indistinguishable from the other types of nonsyphilitic medial aortic involvement.[14]

Review of the necropsy findings in the cases with aortic lesions and arachnodactyly has also shown a high incidence of aortic valvular deformities associated with cardiac hypertrophy.[2, 5, 9, 12, 14] Dilatation of the aortic rings producing aortic regurgitation has been common, but aneurysmal dilatation of the aortic sinuses of Valsalva was reported in only two in-

stances.[10, 17] Valvular and, less commonly, mural thickening, grossly indistinguishable from rheumatic fever lesions, is also common in arachnodactyly. Microscopic study, however, has rarely disclosed the features of rheumatism, and the microscopic lesions have been described as being of a fibromyxomatous character often seen in other types of congenital heart disease.[12, 14]

Clinically, as in cases 1 and 3, the onset of cardiovascular disease probably begins when a systolic murmur is heard during the teens. Later, as in case 1, cardiac enlargement follows. The signs of aortic insufficiency (probably due to the aneurysmal dilatation of the ascending aorta involving the aortic ring) may occur, as in case 2. Congestive heart failure of an intractable nature is often terminal.

The cardiovascular roentgen findings in arachnodactyly are usually meager. As in two of our cases, there may be only cardiac enlargement, especially of the left ventricle. Aneurysmal dilatation of the ascending aorta may be demonstrated.[20]

Congenital aortic sinus aneurysms are rare and, because of their intracardiac location, are seldom diagnosed ante mortem. Morgan Jones and Langley, in their classic paper,[21] collected only 23 cases of proved congenital aortic sinus aneurysms from the literature, and added two of their own. Earlier, Micks reported a case of dilatation of all of the aortic sinuses.[22] Recently a congenital aneurysm of the right aortic sinus of Valsalva was diagnosed by retrograde aortography.[23]

With the advent of angiocardiography the diagnosis of aortic sinus aneurysm during life even before rupture became a clinical possibility.[24] Study of patients with syphilitic aortitis [25] soon led to the discovery of a case of an acquired syphilitic aortic sinus of Valsalva aneurysm.[26, 27] Recently three cases of generalized dilatation of the aortic sinuses associated with coarctation were reported.[28] The total number of cases of aortic sinus aneurysms diagnosed at this center by angiocardiography is now 15; eight, acquired syphilitic; seven, congenital (five of the latter were associated with coarctation of the aorta) and the three herein reported occurring in arachnodactyly.

Aneurysmal dilatation of the aortic sinuses in patients with arachnodactyly must be ascribed to aortic medial degeneration, a condition which seems to be present in almost all adults with the disease. Sudden rupture with death, or the development of an aorticocardiac shunt producing congestive heart failure, is a possibility.[21, 29, 30] More likely, the further dilatation of the sinuses causes aortic ring incompetence (as in case 2) and, later, intractable heart failure results. In any event, the prognosis is grave.

Summary

Angiocardiographic study of three consecutive patients with arachnodactyly disclosed aneurysmal dilatation of the aortic sinuses in each instance. The first case, a man of 40 years, was asymptomatic in spite of cardiac

enlargement of six years' duration. The second case, a 47 year old woman, had sudden onset of chest pain which was followed by dyspnea and weakness, and on examination aortic regurgitation, mild congestive failure and enlargement of the heart were found. The third patient was also asymptomatic; a systolic apical cardiac murmur increased in intensity over a six year period; no heart enlargement was present, however.

Cardiovascular disease occurs commonly in adult patients with Marfan's syndrome. Medial degeneration of the aorta and, rarely, of the pulmonary artery is a constant finding. Aneurysmal dilatation of the ascending aorta, with dissection and rupture or dilatation of the aortic rings and aortic regurgitation and heart failure, is a frequent cause of death. In addition, the presence of fibromyxomatous endocardial lesions is common and may produce murmurs of valvular stenosis or regurgitation.

The demonstration of a sinus of Valsalva aneurysm in arachnodactyly during life has hitherto not been reported. It may be of ominous prognostic significance.

Addendum

Since this paper was submitted for publication, McKusick[81] has also reviewed the cardiovascular aspects of Marfan's syndrome and reported dilatation of the ascending aorta and aortic sinuses associated with mild coarctation of the aorta in one of the four cases studied at necropsy.

Summario in Interlingua

Le studio angiocardiographic de 3 consecutive patientes adulte con arachnodactylia (syndrome de Marfan) revelava dilatation aneurysmal del aortic sinuses (de Valsalva). Arachnodactylia es un morbo hereditari de incognoscite etiologia. Degeneration medial del aorta causa aneurysma dissecante; cambiamentos skeletal resulta in cyphoscoliosis; e dislocation del lentes ocular deteriora le vision. On opina que le morbo es causate per un disturbation del substantia fundamental (texito conjunctive). Le recente production experimental de cyphoscoliosis, disturbation periosteal, e aneurysma dissecante in rattos ponite super un dieta de pisos odorose es attribuite a un disturbate processo formative o a un excesso del destruction de sulfato de chondroitina in le substantia fundamental. Ergo on pote postular que arachnodactylia es un morbo hereditari debite a un defective metabolismo de sulfato de chondroitina.

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FACTORS INFLUENCING THE LATE RESULTS OF MITRAL VALVULOPLASTY FOR MITRAL STENOSIS *

By LAURENCE B. ELLIS, M.D., F.A.C.P., and DWIGHT E. HARKEN, M.D., F.A.C.S., *Boston, Massachusetts*

THE successful surgical correction of mitral stenosis has been a dramatic therapeutic milestone. Sufficient time has now elapsed to prove that surgical intervention may be life-saving. One might even assume, from some of the papers presented and published, that the problem of mitral stenosis has been entirely solved. This, of course, is not so. Stenosis of the mitral valve is but one factor, albeit frequently the dominant one, involved in chronic rheumatic heart disease. The successful surgical attack on this valve does not directly correct many of the other factors. The valve is never returned to the normal anatomic state, though hemodynamically it may approach this.

The first gross assay of a surgical technic is based on the question, Can desperately ill patients survive it? the second, on the question, Are desperately ill patients improved? Most publications to date have dealt with this, essentially a *quantitative* aspect. We are now ready for a *qualitative* assay. We need to know how well the operation has been performed, the specific morphology of the deformed valve, the details of the *primary* and *secondary* stenosis, and the surgeon's impression of how well he dealt with the whole complex. Since the operation itself is a blind one, and the valve cannot be scrutinized before and after surgery by an impartial observer, we must rely substantially on the surgeon's description of the valve at operation assessed against the long-term results of follow-up studies. This is such a study: a clinical study based chiefly on our first 500 valvuloplasty patients who had a preoperative diagnosis of *predominant mitral stenosis without important associated disease.*

SELECTION OF PATIENTS

Increased experience has not substantially altered the criteria for the selection of patients for operation which have been laid down initially,[1] and which are in accord with the opinions of most other authors. We do not believe that patients without significant symptoms (Group I) should undergo surgery merely because they have the murmur of mitral stenosis.

* Presented at the Thirty-sixth Annual Session of the American College of Physicians, Philadelphia, Pennsylvania, April 26, 1955.

From the Thorndike Memorial Laboratory, The Second and Fourth Medical Services (Harvard), Boston City Hospital, the Surgical Service of The Peter Bent Brigham Hospital and the Departments of Medicine and Surgery, Harvard Medical School.

This study was supported by Grant No. 442 from the National Heart Institute.

The second group consists of patients who suffer from some impairment of function, usually dyspnea, which is *not* progressive. These individuals can postpone operation unless they find their limitation unacceptable. If they elect surgery, it carries a very low risk (less than 1%). Many of these Group II patients may never need operation, as mitral stenosis may run a very benign course. There were only 13 of this group in the series of 500.

Group III consists of patients with progressive symptoms. These patients usually have pulmonary difficulty, such as chronic dyspnea or repeated attacks of acute dyspnea or pulmonary edema. Here there is urgent need for operation. These patients (Group III) constituted the majority of this series (342).

There were 145 in Group IV. These were cardiac invalids, most of whom had had chronic congestive failure.

TABLE 1

Duration of Follow-up of the First 500 Patients Undergoing Mitral Valvuloplasty (as of July, 1954)

6 months–1 year	31
1–2 years	230
2–3 years	127
3–4 years	42
4–5 years	10
Total followed	440
Lost	2
Operative deaths	58
Total	500

Mean follow-up time—22 months

Operative Mortality: The figures on operative mortality reflect improvement in medical management of these patients and in surgical technic. In Groups II and III the mortality of 14% in the first hundred has decreased to less than 3% in the fifth hundred. Indeed, *in the last 200 Group III patients* (operated upon after this initial series of 500), *there has been only one operative death,* or a mortality of 0.5%. The improvement reflects the increased skill of the surgeon at the operating table, better anesthesia and improved medical management before and after surgery. The operative mortality in the Group IV patients remains high and is still of the order of 20 to 25%. The gains reflected in Group III patients are canceled in the terminal group by the fact that increasingly ill patients are being brought to surgery.

Follow-up Results: Four hundred forty of the 442 patients who survived operation have been followed for periods ranging from six months to five years, with an average follow-up period of nearly two years (table 1). Since this follow-up study was completed nine more months have elapsed. (The

information that we have regarding patients in this period is in entire agreement with the study, but since it is not complete it is not cited here except as indicated subsequently.) The results have been analyzed by groups and in detail elsewhere.[2] For the purpose of this communication the late results have been combined. Seventy-eight per cent have had worth while improvement (moderate to marked); in the remaining 22% the improvement has been slight, or the patients are unchanged, or worse, or have died.

What are some of the factors which affect the end results? Some of these are inherent in the process of selection of patients; others are related

TABLE 2

Effect of Various Factors on Long-Term Results

Age	
Patients under 40	85% Improved
Patients over 40	70% Improved
Auricular Fibrillation	
Patients in normal sinus rhythm	87% Improved
Patients in auricular fibrillation	70% Improved
Associated Valve Disease	
Patients without associated valve disease	80% Improved
Patients with associated valve disease	69% Improved
Associated Mitral Insufficiency Found at Operation	
Patients without mitral insufficiency	82% Improved
Patients with mild insufficiency	82% Improved
Patients with moderate to marked insufficiency	63% Improved
Estimated Valve Size at Operation	
Less than 1.0 sq. cm.	81% Improved
More than 1.0 sq. cm.	70% Improved
Postoperative Valve Size	
More than 2.5 sq. cm.	81% Improved
Less than 2.5 sq. cm.	51% Improved
Calcification of Mitral Valve	
Patients without calcified valve	81% Improved
Patients with calcified valve	66% Improved

to the state of the mitral valve as found at operation, and the surgeon's success in effecting an adequate valvuloplasty (table 2).

As expected, older patients have fared less well than younger. As a group they have had their disease longer, they are sicker, and more irreversible changes have often occurred in the myocardium, lungs and liver. The valves are more often calcified and difficult to mobilize. Associated degenerative diseases, especially atherosclerosis, are more advanced. That the older patients have done less well than the younger is not so remarkable as the fact that *70% of these older patients have improved.* This will be found in all of the analyses to be discussed below. In every instance a majority

of the patients in the least successful category showed worthwhile improvement.

The patients with auricular fibrillation have done less well than those in normal sinus rhythm. In part this is due to greater age and more severe clinical symptoms in these patients, but this does not completely explain the difference.

None of the patients in this series had a severe grade of associated valvular disease, but many had some evidence of aortic valve involvement as judged by "aortic" diastolic or systolic murmurs. These have had a less favorable outcome as a group than those with mitral valve involvement alone.

The greatest problem in the selection of patients for operation lies in the clinical estimation of the presence of mitral insufficiency in these patients. The criteria used in determining insufficiency in the presence of mitral stenosis have been discussed elsewhere.[8] We still lack a perfect test for this prior to surgery. The most reliable test for insufficiency is palpation by the surgeon at operation. Even this is imperfect, particularly if the blood pressure is low at the time of palpation. However, with this as the final arbiter, an operative finding of pure stenosis without insufficiency had been correctly anticipated in 86% of the cases, but when significant insufficiency was found at operation there had been a correct preoperative diagnosis in only 64% of the patients. There were 75 such patients. A mild degree of insufficiency found at operation did not affect the ultimate good prognosis. If a greater degree was present the patients did somewhat less well, but still 63% were helped. It must be remembered that in most of these patients significant mitral stenosis was present and surgically corrected.

The best results were found in the patients with the greatest degree of stenosis. Using an area of 1 square centimeter (as estimated by the surgeon at operation) as the dividing line between tight stenosis and that which is less severe, 81% of those in the former group were helped, as compared to 70% in the latter group.

Similarly, the better the surgeon was able to mobilize the valve leaflets the better the results. Here again, an estimated area of 2.5 sq. cm. was considered the minimal degree of valve opening which was satisfactory.

The patients with calcified valves did less well than those without calcification. Presumably such calcified valves on the whole lend themselves less well to fracture and mobilization.

These findings support and emphasize the thesis that the major symptoms stem from the altered hemodynamics of the *mitral stenosis per se*. Thus, with a severe degree of narrowing of the valve, it is likely that this is the major cause of the disability, and the opportunity for relief by adequate valvuloplasty is great.

The various factors affecting the late results have been considered together. These adverse factors are: (1) age over 40; (2) auricular fibrillation; (3) some associated aortic valve involvement; (4) associated mitral

insufficiency of moderate degree or more; (5) a preoperative valve size of more than 1.0 sq. cm.; (6) a postoperative valve size of less than 2.5 sq. cm.; (7) calcification of the mitral valve. These criteria were arbitrarily selected since they can be determined with some accuracy before or at operation.

Table 3 shows the cumulative effect of an increasing number of such adverse factors on the outcome. If none was present there was almost the certainty of significant improvement (96%), and with an increasing number of factors the outcome became progressively less favorable; with five factors only one-half of the patients improved. In no patient were more than five adverse factors present. Thus it can be seen that the likelihood of a successful end result can be predicted percentage-wise by a consideration of certain determinable factors.

Fourteen patients developed recurrences of active rheumatic fever at some point in their follow-up period. Of these, nine were unimproved.

Peripheral Embolization: One of the real problems in the evaluation of patients for operation is the effect of the operation on peripheral emboliza-

TABLE 3

Relation of Number of Adverse Factors to the Improvement of Patients with Mitral Stenosis (See text for description of factors)

No. of Adverse Factors	Groups II and III		Group IV		Total	
	No. of Patients	% Improved	No. of Patients	% Improved	No. of Patients	% Improved
0	89	96	1	100	90	96
1	95	89	24	75	119	87
2	75	71	37	76	112	72
3	41	73	25	56	66	67
4	21	57	13	54	34	56
5	10	60	4	25	14	50

tion. Although all patients with mitral stenosis in auricular fibrillation are liable to this complication, the problem is usually presented when a patient has already had one or more peripheral emboli. In this series of 500, there were 79 such patients. All but eight were in auricular fibrillation at the time of operation, and some of these eight had had paroxysmal fibrillation in the past. None of the eight developed emboli at the time of operation, but 17 of the 71 in auricular fibrillation did, an incidence of 25% (19% in Group III, 33% in Group IV), as compared to an over-all percentage of embolization of 5.6 in Group III and 16 in Group IV. In the next 300 patients operated upon since this series, there have been six operative emboli in 60 patients who had had preoperative episodes, or 10% (5% in Group III, 20% in Group IV). The incidence of operative emboli in these 300 patients has been 2.8% in Group III and 11% in Group IV. Thus the possibility of operative embolization has been significantly decreased as our experience has increased, but it still remains a little higher in patients who

have had previous emboli than in the series as a whole. The judgment involved in the avoidance of operative emboli at the price of doing too little for the patient's mitral stenosis will be discussed fully in another publication.

If the patient surmounted the hurdle of the operation the danger of a late peripheral embolus is small. Only five of the 442 surviving patients from the series of 500, during the follow-up period of the study averaging 22 months, suffered late emboli, although more than half of them were fibrillating. In the nine months which have elapsed since this follow-up study was made, one more peripheral embolus has been observed in this group. In the 300 operations analyzed since the pilot group of 500 there have been two late emboli. We believe that the operation decreases the possibility of late peripheral embolization substantially. Glover et al.[4] have reported an even more favorable experience with late embolization, having had only one out of 500 patients.

When a patient who is undergoing evaluation for surgery has had one or more peripheral emboli and is also suffering from significant disability in exercise tolerance secondary to the mitral stenosis, the indications for operation are clear-cut. If the patient has no effort limitation but has had previous emboli, the decision is more difficult and must be weighed against alternative methods of therapy, but it is our belief that operation will prove in these cases to be the best procedure.

Regressions: Very few of the patients in the series have regressed after an initial improvement persisting six months or longer. There has been only one patient in Group II, 18 in Group III and 12 in Group IV, a total of 31. In 15, one or more factors were present which might explain this regression, such as: associated aortic valvular disease, poor operative fracture of leaflets which could not be mobilized by technics then available, significant mitral insufficiency found to be present at the time of operation, or rheumatic fever occurring after operation. In five we lack adequate information. There are 11 regressions in which a possible explanation is not apparent. It may be that re-fusion of the commissures has occurred in some of this group, with resultant reconstitution of the mitral stenosis. It is also possible that dilatation, not valvuloplasty, was carried out. In the past few years we have become increasingly conscious of stenosis beyond the primary fusion of the leaflets. This distal fusion of chordae tendineae and papillary muscles is called *"secondary stenosis."* Valvuloplasty constitutes the surgeon's best effort at total valve restoration; dilatation is frank failure, and commissurotomy only part of the procedure.

Since we do not know as yet the factors which led to the production of tight mitral stenosis in the first place, usually many years after the initial rheumatic fever, it is too early to claim that mitral stenosis may not recur in some instances after operation. Our follow-up studies indicate, however, that if this does occur it is uncommon and rarely to a degree sufficient to result in recurrent symptoms within the period of observation.

This again points up the necessity of emphasizing the quality of the

operative procedure that is performed, something which unfortunately can be fully gained only through extensive experience. Glover and associates [5] have also emphasized this necessity for a qualitative approach, and have pointed out the rarity of the reformation of the mitral stenosis.

Objective Findings: The objective clinical findings have been studied in a group of 106 of these patients observed one or more years after operation. These will be reported in detail elsewhere.

There were no consistent or striking changes, nor any clear-cut correlations between such changes as did occur and the degree of improvement in exercise tolerance of the patients.

The heart size, as judged by careful fluoroscopic and roentgenologic study carried out before and after operation in 53 patients, did not alter materially. In 12 out of 53 patients there was a decrease in size of the pulmonary artery, and in 14 patients the left auricle became smaller. In six patients the pulmonary artery and in nine the left auricle increased in size. The right ventricle became demonstrably smaller in 12 patients and larger in 10. In only two patients did the left ventricle appear to increase in size.

There was similarly no consistent change in heart murmurs. In 60 of 104 patients the apical diastolic murmur became less marked, but the change was usually slight. Only 10 times did it disappear altogether. An apical systolic murmur increased or appeared for the first time in 30, and decreased or disappeared in 16. A blowing diastolic murmur, loudest parasternally, was present preoperatively in 25 patients. It was unchanged in 17, decreased in eight, and became louder in none. Such a murmur made its first appearance postoperatively in only two patients.

The electrocardiogram also showed little change of importance. P waves became smaller in over half the patients in normal rhythm. In no instance did a definite left ventricular enlargement pattern develop postoperatively. Evidence of right ventricular strain or enlargement often diminished.

Discussion

The fact that mitral valvuloplasty can now be successfully carried out with a very low mortality in Group III patients, but still carries a substantial risk (20 to 25%) in Group IV, points up the desirability of getting patients to surgery before they reach this terminal state. This does not mean that patients without significant symptoms should be urged to have operation. The life history of mitral stenosis is such that most patients, if carefully followed, can be selected for surgery at the time their deterioration becomes progressive but before complete breakdown or irreversible damage has occurred. Rarely, patients will slip from an almost symptomless phase directly and rapidly into chronic congestive failure. When this occurs, myocardial failure rather than stenosis of the mitral valve is usually the dominant factor in the breakdown. It is the authors' experience that in this particular group operation is usually of little value. We still have much to learn about the

state of the myocardium in patients with mitral stenosis. It is generally assumed either that we are dealing with a myocardium damaged by *active* rheumatic infection, or that we have an essentially normal myocardium which fails only as the result of physiologic strain secondary to the burden of the raised pulmonary pressure back of the stenosed mitral valve, plus the impaired blood flow. There is too little reflection on the possibility that a myocardium may be permanently weakened by the ravages of burnt-out rheumatic infection, and that such a heart may succumb to heart failure when relatively slight mechanical strain in the form of stenosis is imposed upon it. Further studies bearing on this point are indicated. Such myocardial failure may be of particular importance in patients in whom marked mitral insufficiency is present. The insufficiency in some of these patients may be largely secondary to an enlarged annulus, which is part of this general state of cardiac dilatation consequent on myocardial failure. In such patients correction of the mitral insufficiency by operation is no more likely to help than it would if done on a patient with a dilated heart in myocardial failure of arteriosclerotic origin.

The follow-up study that has been reported indicates that worth while improvement occurs following mitral valvuloplasty in 78% of patients, and that the results in Group IV are surprisingly gratifying (63% improved), considering the seriousness of the preoperative condition of the patients. Though very good, these results are not so striking as the results in Group III (81% improved). The outstanding results in Group III constitute a firm basis for urging operation at this stage of the disease.

The criticism has been made by some that the reported improvement that occurs might be due to the psychic effects of the dramatic procedure, to the natural variation in the course of the disease, or to improved medical treatment. If these were the dominant factors it is unlikely that the best results would take place in those patients where tight mitral stenosis has been adequately corrected by operation. Our analysis establishes this. Moreover, the fact that the improvement tends to be progressive over many months and lasting in most cases is against the psychologic basis of benefit. The conclusion is inescapable that the operation confers a genuine and frequently dramatic benefit to properly selected patients. This improvement is usually persistent over the period of follow-up observation, and can be properly ascribed to the mitral valvuloplasty itself. In addition, there is evidence that the operation protects significantly against the possibility of peripheral embolization. Although this operation has great value, it must be remembered that it is still a palliative procedure, frequently a dramatic and life-saving palliation, but only an important part of the over-all treatment.

Summary

A study is reported of various factors that affect the late results in patients with mitral stenosis operated by mitral valvuloplasty. This study

is based chiefly on a follow-up of the first 500 patients. Seventy-eight per cent of the patients surviving operation showed significant and usually persistent improvement over the period of observation, which averaged 22 months. The factors which led to less good results were (1) age over 40; (2) auricular fibrillation; (3) associated aortic valve disease; (4) associated mitral insufficiency of moderate degree or more; (5) a preoperative valve size of more than 1.0 sq. cm.; (6) a postoperative valve size of less than 2.5 sq. cm.; (7) calcification of the mitral valve. Even in the less successful categories the over-all results were still good in a majority of the patients. Poor late results occurred in direct proportion to the number of adverse factors present.

The operative mortality in Groups II and III is now less than 3% and appears to be below 1%. It is 20% in Group IV. The procedure appears to protect substantially against late peripheral embolization, although the incidence of operative emboli is somewhat greater in patients who have had previous emboli than in the groups as a whole. Good end results depend on intelligent and careful selection of patients and on the quality of the valvuloplasty performed by the surgeon.

Summario in Interlingua

Es reportate un studio de varie factores que affice le resultatos permanente de valvuloplastia in patientes de stenosis mitral. Le studio se basa principalmente super observationes del curso post-operatori de nostre prime 500 patientes. Ex le total del patientes qui superviveva le operation, 78 pro cento monstrava significative e usualmente persistente melioration durante le periodo de observation que amontava a un duration median de 22 menses. Le factores que esseva responsabile pro minus satisfacente resultatos esseva (1) etate de plus que 40 annos, (2) fibrillation auricular, (3) associate morbo del valvula aortic, (4) associate insufficientia mitral de grado moderate o sever, (5) pre-operatori dimension valvular de plus que 1,0 cm quadrate, (6) post-operatori dimension valvular de minus que 2,5 cm quadrate, e (7) calcification del valvula mitral. Mesmo in le categorias a successo restringite, le resultatos general esseva ancora satisfacente in le majoritate del casos. Le minus satisfacente resultatos permanente occurreva proportionalmente al numero del adverse factores presente.

Le mortalitate operatori inter le 145 plus sever casos—includente solmente "invalidos cardiac" qui habeva habite, con pauc exceptiones, chronic dysfunctionamento congestive—esseva 20 pro cento. Inter le alteres le mortalitate esseva 14 pro cento pro le prime quinto del integre serie e 3 pro cento pro le quinto final. (Inter le casos operate post le periodo del presente reporto, le correspondente mortalitate ha cadite a infra 1 pro cento.)

Valvuloplastia in stenosis mitral pare representar un efficace protection contra tardive embolisation peripheric ben que le frequentia de embolos operatori es alique plus alte inter patientes con experientias embolic que in le serie integre. Bon resultatos terminal depende del qualitate del labor executate per le chirurgo.

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UNUSUAL MANIFESTATIONS OF DISSEMINATED LUPUS ERYTHEMATOSUS * †

By GORDON C. MEACHAM, M.D., and AUSTIN S. WEISBERGER, M.D.,
Cleveland, Ohio

SINCE the discovery of the L.E. test [1] as a highly specific diagnostic procedure, our knowledge of the clinical course and manifestations of disseminated lupus erythematosus has increased markedly. It has become apparent that this disease may present itself in an atypical manner which may precede the onset of clinically recognizable disseminated lupus erythematosus by many years. This is particularly true of hematologic manifestations such as thrombocytopenic purpura, hemolytic anemia and clotting abnormalities. It is also evident that the disease is not necessarily rapidly and progressively fatal, but may be one of spontaneous remissions and exacerbations as well as prolonged periods free of detectable disease.[2, 3]

Because of the changing concepts concerning this disease, it has become necessary to reëvaluate the diverse clinical and laboratory findings which may be present in this disease. The purpose of this report is to summarize some of the unusual manifestations of disseminated lupus erythematosus seen at this hospital since the advent of the L.E. test.

CASE MATERIAL

The case material includes all patients with this disease seen at this institution during the past five years. Of the 25 patients in this series the diagnosis was confirmed by a positive L.E. test in 24, one case being proved at autopsy. In all instances the L.E. test was performed on peripheral blood according to the method previously described.[4] In most cases it was not necessary to add fibrinogen because of the associated rapid sedimentation rate; in four instances normal sedimentation rates were found, and in these fibrinogen was used to increase the sedimentation rate. Tests using marrow or clotted blood showed no greater specificity. The onset of the disease was considered to date from the time the patient first had signs or symptoms of manifestations which we now consider to be part of the symptom complex of disseminated lupus erythematosus.

RESULTS

The initial manifestations of the disease in this series of patients included purpura, skin rash, arthritis, pericarditis, fever, false-positive serologic test

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From the Department of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.
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for syphilis, Raynaud's phenomenon or albuminuria (table 1). In 11 of the 25 cases the initial clinical findings were so characteristic that there was little doubt as to the diagnosis before it was confirmed by the L.E. test.

Several patients presented themselves with manifestations which are not usually considered to be part of this disease. Thus three patients were first diagnosed as idiopathic thrombocytopenic purpura and subjected to splenectomy. Similarly, a circulating anticoagulant, a false-positive serologic test for syphilis, and Raynaud's phenomenon as isolated findings preceded the typical findings of disseminated lupus by from four months to 13 years. In other cases these findings were present at the time the patients initially presented themselves with the typical disease. In one patient intestinal

TABLE 1

Case Number	Duration of Disease (Years)	Initial Manifestation
1	1¾	Purpura
2	9	False-positive serology
3	5	Raynaud's phenomenon
4	½	Albuminuria
5	17	Pericarditis
6*	1½	Arthritis
7*	1	Fever
8*	½	Rash
9	3	Arthritis
10*	2	Arthritis
11*	4	Arthritis
12	2	Arthritis
13	7	Purpura
14	½	Fever
15	2	Rash
16	4	Arthritis
17	3	Albuminuria
18	5	Rash
19	11	Purpura
20*	8	False-positive serology
21	2	Arthritis
22	1	Rash
23	8	Fever
24*	½	Arthritis
25	13	Raynaud's phenomenon

* Denotes patients who have died.

perforation led to the diagnosis; anemia and pericarditis antedated this event by 17 years (see case 5).

Various hematologic abnormalities were present in these cases. Thus during the course of the disease five patients had thrombocytopenic purpura, two had a circulating anticoagulant, four had hemolytic anemia, and eight had a positive Coombs' test. Absolute leukopenia or relative leukopenia in the presence of fever was a common finding.

A marked variation in duration of the disease, in onset of initial manifestations to death or to the present time, was present in this group. Seven patients have died and 18 are still living. Of the seven who died, the average duration was 2.6 years, whereas of those still living eight have had the disease for five years or longer, and two cases have survived 13 years

and 17 years, respectively (table 1). These findings are indicative of the marked variation in severity and duration of the clinical course of this disease, as has been noted by others.[2, 3]

Case reports illustrating some of the unusual manifestations follow:

Case Reports

Case 1. "Idiopathic" thrombocytopenic purpura preceding disseminated lupus erythematosus.

A 59 year old white female was admitted to the University Hospitals of Cleveland on May 15, 1952, because of purpura of three weeks' duration. Physical examination revealed pallor and petechial and ecchymotic lesions over the legs and, to a lesser extent, over the arms. The remainder of the physical examination was normal. Laboratory data were as follows: erythrocyte count, 1,850,000 cells per cubic millimeter; hemoglobin, 4.8 gm. per 100 c.c.; hematocrit, 16%; leukocyte count, 8,600 cells per cubic millimeter, with a normal differential count. The platelet count was 3,000 cells per cubic millimeter. Studies for the presence of hemolytic anemia were negative. Sternal marrow aspiration revealed erythroid hyperplasia and increased numbers of megakaryocytes, many of which were immature. Examination of the stools for occult blood was positive. Because of the development of bleeding from the nose and gums and an increase in the purpura, a splenectomy was performed on the seventh hospital day. The spleen was normal in size; histologic examination revealed only focal hemosiderosis.

Postoperatively the platelet count did not increase. The patient was started on cortisone therapy, and blood transfusions were given when indicated. Because stool examinations continued to show occult blood, radiologic examination of the gastrointestinal tract was done which revealed a small filling defect on the lesser curvature of the stomach. On June 6 a subtotal gastrectomy was performed; histologic examination revealed a partially differentiated adenocarcinoma of the stomach. The patient's postoperative course was benign, and she was discharged on June 16, 1952.

She was next seen on October 19, 1953. At that time she had no complaints. Laboratory studies were as follows: erythrocyte count, 4,010,000 cells per cubic millimeter; hemoglobin, 11.3 gm. per 100 c.c.; hematocrit, 38%; leukocyte count, 4,300 cells per cubic millimeter. The platelet count at this time was 360,000 cells per cubic millimeter. On February 1, 1954, the patient was re-admitted because of fever of two months' duration. Physical examination at this time revealed generalized adenopathy, with involvement of cervical, axillary and inguinal areas. Laboratory data revealed lymphoid and reticuloendothelial hyperplasia. During the first 10 hospital days the patient's temperature varied between 37.5° and 39.5°. At this time, because of the history of thrombocytopenic purpura and the unexplained adenopathy, an L.E. test was performed which was strongly positive. On cortisone therapy the patient made an uneventful recovery and has subsequently remained asymptomatic.

Case 2. Hemolytic anemia as an initial manifestation and a false-positive serologic test for syphilis for seven years.

A 28 year old white female was admitted to the University Hospitals of Cleveland on February 17, 1952, complaining of swelling of both hands of three months' duration. During this time she had noticed occasional paresthesias of her hands, transient arthralgia and progressive fatigue. Seven years previously she had been found to have a false-positive serologic test for syphilis. Pertinent physical findings were erythematous atrophic lesions on the nose and sides of the fingers, and mild splenic enlargement. Laboratory data revealed the following: erythrocyte count, 2,840,000 cells per cubic millimeter; hemoglobin, 7.8 gm. per 100 c.c.; hematocrit, 27%; leukocyte count, 4,400 cells per cubic millimeter; platelet count, 240,000 cells per cubic

millimeter. Differential cell count, bleeding and clotting times were within normal limits. The reticulocyte count was 3.3%. An L.E. test was positive. Serologic tests for syphilis revealed a positive Kline test but a negative Wassermann. The patient was given an eight day course of ACTH, and two 500 c.c. blood transfusions, and discharged improved.

On April 12, 1952, she was re-admitted to the hospital because of fever of six days' duration. Aside from a temperature of 39°, physical examination was essentially unchanged. Laboratory data were as follows: erythrocyte count, 2,600,000 cells per cubic millimeter; hemoglobin, 7.8 gm. per 100 c.c.; hematocrit, 25%; leukocyte count, 7,900 cells per cubic millimeter, with a normal differential count. Reticulocyte count was 3.6%.

During the next seven days a marked exacerbation of the hemolytic process occurred; on April 19 laboratory studies were as follows: erythrocyte count, 1,240,000 cells per cubic millimeter; hemoglobin, 4.8 gm. per 100 c.c.; hematocrit, 13%. Examination of the blood films revealed marked spherocytosis and phagocytosis of erythrocytes by monocytes and neutrophils in the peripheral blood. The reticulocyte count was 15.2%. Serum bilirubin was 2.2 mg. % total, 0.6 mg. % direct. Fragility studies revealed increased osmotic fragility of the patient's erythrocytes. Coombs' test was positive up to a dilution of 1:1024; the indirect Coombs' test was positive in a dilution of 1:128. Cold agglutinins were positive in a dilution of 1:32. On cortisone and blood transfusions the patient responded well and was discharged on the twenty-first hospital day. Subsequently she has been maintained on oral cortisone therapy, 50 to 75 mg. daily; she has remained asymptomatic, and the hemolytic process is apparently controlled.

Case 3. Raynaud's phenomenon and circulating anticoagulant as initial manifestations of disseminated lupus erythematosus.

A 41 year old white female was first admitted to the University Hospitals of Cleveland on July 19, 1949, because of painful and cyanotic left fourth and fifth fingers of two months' duration. A left thoracic sympathectomy was performed, with subjective and objective improvement. However, pain and cyanosis of the fingers recurred, and four weeks later amputation of the two distal phalanges of the left fingers was performed. The pathologic diagnosis at this time was proliferative endarteritis and organizing thromboses of arteries, etiology undetermined.

In December of 1949, she was admitted because of pain in her legs on exertion. Physical examination at that time revealed mild hepatosplenomegaly. Laboratory studies were as follows: erythrocyte count, 3,630,000 cells per cubic millimeter; hemoglobin, 7.5 gm. per 100 c.c.; hematocrit, 25%; leukocyte count, 4,200 cells per cubic millimeter, with a normal differential count. Clotting time was 28 minutes (Lee-White). The patient refused further studies and was discharged.

She was re-admitted in March, 1950, because of a pyogenic ulcer over the right lateral malleolus. At this time there was no essential change in the physical examination. Laboratory studies were as follows: erythrocyte count, 3,470,000 cells per cubic millimeter; hemoglobin, 7.6 gm. per 100 c.c.; hematocrit, 24%. The leukocyte count and differential studies were within normal limits. The reticulocyte count was 1.1%. The clotting time was 20 minutes (Lee-White). Routine blood chemistry studies revealed an elevated globulin and a 4 plus cephalin flocculation test. One L.E. preparation was reported as positive, but a subsequent test was reported as negative. Skin biopsy revealed widespread arteriolar thrombi and focal chronic arteriolitis. The leg ulcer responded to therapy, and the patient was discharged without a specific diagnosis as to the underlying disease.

On August 30, 1951, the patient was re-admitted because of ascites. The liver was slightly more enlarged than on previous admissions. Laboratory data revealed a Bromsulphalein retention of 20% in 45 minutes; cephalin flocculation test, 4 plus;

thymol turbidity, 7.8 units. The patient refused further studies after a paracentesis was performed, and was discharged.

She was re-admitted on February 8, 1954, because of progressive weakness of the legs. Hepatosplenomegaly remained unchanged. Mild sacral and pretibial edema was present, but there was no sign of intraperitoneal fluid. Laboratory data at this time were as follows: erythrocyte count, 4,340,000 cells per cubic millimeter; hemoglobin, 12.0 gm. per 100 c.c.; hematocrit, 37%; leukocyte count, 3,800 cells per cubic millimeter, with a normal differential count. A prolonged clotting time and a circulating anticoagulant active against human brain thromboplastin were demonstrated by Dr. Oscar Ratnoff. Repeated L.E. tests were positive. She was discharged on the tenth hospital day.

Case 4. False-positive serologic test for syphilis leading to the diagnosis of disseminated lupus erythematosus.

A 17 year old white female was admitted to the University Hospitals of Cleveland on June 16, 1954, because of albuminuria of two months' duration. On physical examination the blood pressure was normal; there was mild pretibial edema, but no other abnormalities were noted. Laboratory findings revealed normal blood counts. Routine blood chemistries were normal. Urinalysis revealed 4 plus albuminuria, without other abnormalities. Serologic studies revealed a 4 plus Wassermann and a 4 plus Kline reaction, the titer of the latter being negative at 1:20. A diagnosis of syphilitic nephrosis was suggested, but because it was thought that the serologic reaction was a false-positive, an L.E. test was done which was markedly positive.

Case 5. Signs and symptoms suggestive of disseminated lupus erythematosus for 17 years; intestinal perforation leading to a diagnosis of disseminated lupus erythematosus.

A 33 year old white female was admitted to the University Hospitals of Cleveland on April 27, 1941, complaining of substernal pain and pain in the left shoulder and left hand. In 1937 she had been admitted to another hospital, at which time a diagnosis of "pneumonia, pericarditis, and severe anemia" had been made.

Physical examination and laboratory studies were normal. Histologic examination of a muscle biopsy revealed subacute angiomyositis. During the next 11 years the patient was re-admitted on 10 different occasions. During this time she had intermittent chest pain and joint pain, menometrorrhagia, parotid swelling and pneumonitis.

On March 25, 1953, she was admitted with severe abdominal pain. Exploratory laparotomy revealed widespread multiple abscesses secondary to a perforation of a sigmoid diverticulum. On antibiotic and supportive therapy this patient made a gradual recovery. Two weeks later, however, she was re-admitted because of progressive weakness, dyspnea and fever. On admission the temperature was 40.0° C.; the abdomen was slightly tender. Laboratory studies were as follows: erythrocyte count 3,110,000 cells per cubic millimeter; hemoglobin, 9.2 gm. per 100 c.c.; hematocrit, 32%; leukocyte count, 3,750 cells per cubic millimeter, with a normal differential count. Blood chemistry studies revealed only an elevated serum globulin. Blood cultures were negative. During the next six days the marked pyrexia persisted. Because of the history of arthralgia, pericarditis, pneumonitis, anemia, and a biopsy revealing vascular disease, in addition to the elevated globulin, fever and leukopenia, an L.E test was done which showed many typical L.E. cells and rosettes. On cortisone therapy the patient made a rapid recovery and was discharged.

Discussion

One of the most important characteristics of disseminated lupus erythematosus is its ability to manifest itself as other diseases. It is apparent

that to make the diagnosis in a given case one must be aware not only of the variable course but also of the multiplicity of clinical syndromes this disease may simulate. The most common clinical findings in this disease are well known. These consist of fever, involvement of the skin and serous surfaces, alopecia, renal and ocular signs, mild to moderate adenopathy, splenomegaly, leukopenia, elevated serum globulin, and predominance in females.

However, early manifestations of this disease may be obscure. Thus, in this series of cases thrombocytopenic purpura, hemolytic anemia, the presence of a circulating anticoagulant, a false-positive serologic test for syphilis, Raynaud's phenomenon and intestinal perforation were seen either

TABLE 2

Condition	Number of Cases	Per Cent of Total
1. Thrombocytopenic purpura	5	20
2. Hemolytic anemia	4	16
3. Circulating anticoagulant	2	8
4. False-positive serology	7	28
5. Raynaud's phenomenon	5	20
6. Intestinal perforation	1	4

as the initial manifestation of the disease or during its course (table 2). Case 1 demonstrates that thrombocytopenia may be the initial sign of the disease and may precede the onset of clinically recognizable disseminated lupus erythematosus by several years. In three instances a diagnosis of "idiopathic thrombocytopenic purpura" was made 21 months, seven years and 11 years, respectively, before the diagnosis of disseminated lupus erythematosus was established (table 3). In each instance splenectomy was followed by a return of the platelet count to normal limits, this response being immediate in one case and delayed in the other two. Although

TABLE 3

Duration between Time at Which Diagnosis of Idiopathic Thrombocytopenic Purpura Was Made and the Diagnosis of Disseminated Lupus Erythematosus Established

Case Number	Years
1	1¾
13	7
19	11

review of sections of the spleens from two of these cases revealed no definite evidence of disseminated lupus erythematosus, it is well known that thrombocytopenic purpura may be a manifestation of this disease,[5, 6] and it seems quite likely that these three cases had disseminated lupus erythematosus at the time thrombocytopenia was first detected. Two cases developed thrombocytopenia after the diagnosis of disseminated lupus had been established.

Case 2 illustrates that hemolytic anemia may occur early in the course of the disease and that severe hemolytic crises may subsequently develop. Hemolytic studies revealed a positive direct and indirect Coombs' test,

thus demonstrating the presence of an auto-antibody in the serum. In three other instances of hemolytic anemia encountered in this series, the Coombs' test was positive. It should be pointed out, however, that the Coombs' test may be positive in cases of disseminated lupus erythematosus in which there is no evidence of hemolysis,[7] as was found in four cases in this series.

Case 3 represents an instance of disseminated lupus in which a circulating anticoagulant was found. In this series there was one other case showing this phenomenon. This finding has previously been reported,[8] and without exception the anticoagulant has been antithromboplastin in type. Furthermore, to the authors' knowledge, this type of circulating anticoagulant occurs in no other disease entity. It is our belief that the detection of this type of clotting abnormality is highly suggestive of the presence of disseminated lupus erythematosus.

Case 4 demonstrates the importance of recognizing that a false-positive serologic test for syphilis may occur as an initial manifestation of this disease.[9] While it is well known that this may occur in other diseases, any patient showing an unexplained false-positive serologic test for syphilis should be investigated for the presence of disseminated lupus erythematosus, especially when other signs or symptoms suggestive of this disease are present. It seems likely that this phenomenon is due to an abnormal protein or is a manifestation of an abnormal immunologic process; it should be noted that, of the seven cases in this series with a false-positive serologic test for syphilis, four exhibited hematologic abnormalities (i.e., thrombocytopenic purpura, hemolytic anemia or a circulating anticoagulant).

A history of Raynaud's phenomenon was present in 20% of this series of cases. Although it is well known that this may occur in disseminated lupus erythematosus, it is important to emphasize that initially this phenomenon may be the only clinical manifestation of the disease. It is our impression that in many instances Raynaud's phenomenon is a manifestation of an underlying disease process such as disseminated lupus erythematosus or scleroderma; in such cases a thorough trial on medical management is indicated before sympathectomy is performed.

Case 5 illustrates an instance of disseminated lupus erythematosus in which intestinal perforation occurred. Although histologic evidence that the perforation was secondary to a lesion of disseminated lupus is lacking, it is our impression that this complication may occur during the course of this disease. The fact that two cases of intestinal perforation due to periarteritis nodosa have been seen at this institution during the past two years supports this impression. It should be pointed out that in none of these instances were these patients on steroid therapy at the time of the perforation.

At the present time it is our belief that a positive L.E. test (i.e., the presence of L.E. cells and rosettes) is diagnostic of disseminated lupus erythematosus. Although positive L.E. tests have been reported in association

with other diseases and in certain drug reactions,[10, 11] we have not encountered this in our experience. It is possible that in those cases of positive L.E. tests found in association with drug hypersensitivity the patients had latent disseminated lupus erythematosus before the drug was administered; proof as to whether these cases actually had a false-positive L.E. test at the time of the drug reaction or actually had disseminated lupus erythematosus can be obtained only by follow-up studies. In our experience no false-positive L.E. tests have been encountered, and in all cases in which a positive L.E. test has been found the subsequent course has been compatible with this diagnosis.

Negative L.E. preparations, however, do not rule out the presence of this disease, and it is often necessary to repeat the test at frequent intervals before the diagnosis is confirmed. In this series the presence of rosettes alone was not considered diagnostic. In some instances the presence of large numbers of characteristic rosettes, together with the clinical findings, was strongly suggestive. Many such patients with a presumptive diagnosis of disseminated lupus erythematosus were not included in this series because L.E. cells have not as yet been demonstrated; undoubtedly in most of these cases the diagnosis is correct; but, as of the present, clinical verification is lacking. However, in light of increasing experience with the variability of the course of this disease, it seems a reasonable assumption that disseminated lupus erythematosus may be present for long periods of time before a positive L.E. test is found, and that the L.E. test is more frequently positive where there is an exacerbation of the disease.

Kampmeier and Smith [18] have objected to this interpretation, stating: "It seems better to accept a disease process with recurrent exacerbations of tissue sensitivity manifested by arteritis, eventually culminating in a response possibly characterized by a globulin factor which has the ability to produce the L.E. phenomenon, rather than to make the L.E. cell the diagnostic criterion." Such cases would be defined as diffuse recurrent arteritis rather than disseminated lupus erythematosus because, previous to the finding of a positive L.E. test, "the circumstances at no time fitted the diagnosis." Experience with the L.E. test, however, has widened the clinical concepts of this disease and revealed characteristics of the disease unrecognized clinically before the advent of the test. Cases showing a prolonged course before a positive L.E. test is found emphasize the striking variability in the course of the disease, and no advantage is to be gained by describing these cases under another name. Experience has shown that if repeated L.E. tests are done in these cases, especially at the time of an exacerbation, positive tests will often be found. It is our opinion that the L.E. test has clarified, not confused, our clinical understanding of disseminated lupus erythematosus.

It is well known that most of the pathologic lesions of disseminated lupus erythematosus are similar to those found in the anaphylactoid type of

hypersensitivity reactions produced in animals,[12] thus suggesting that this disease may be a manifestation of an abnormal immunologic phenomenon. The L.E. cell itself may be considered the result of an immunophagocytic phenomenon, and hemolytic anemia and thrombocytopenic purpura have been shown in many instances to be secondary to abnormal immunologic reactions.[7] These findings lend further emphasis to the theory that disseminated lupus erythematosus is due to hypersensitivity to an as yet unknown agent.

Conclusions

1. Twenty-five cases of disseminated lupus erythematosus seen at this hospital during the past five years are reviewed.

2. The marked variation in the clinical manifestations and course of this disease is noted.

3. In this series five cases had thrombocytopenic purpura; four had hemolytic anemia; two had circulating anticoagulants; seven had false-positive serologic tests for syphilis, and five had Raynaud's phenomenon. One case developed intestinal perforation. It is emphasized that these conditions may be the initial manifestation of disseminated lupus erythematosus and occur alone long before other manifestations of this disease are present.

4. The specificity of the L.E. test and the rôle of anaphylactoid type of hypersensitivity in the production of disseminated lupus erythematosus are discussed.

Summario in Interlingua

Es presentate un revista del 25 casos de disseminate lupus erythematose vidite al Hospitales Universitari de Cleveland in le curso del passate 5 annos. Es notate le marcate variationes del manifestationes clinic e del curso de iste morbo. In le presente serie 5 patientes habeva purpura thrombocytopenic, 4 habeva anemia hemolytic, 2 habeva anticoagulantes circulante, 7 habeva pseudo-positive tests serologic pro syphilis, e 5 habeva le phenomeno de Raynaud. Un del patientes disveloppava perforation intestinal. Nos sublinea le facto que iste conditiones pote esser le manifestationes initial de disseminate lupus erythematose e como tal pote occurrer sol multo ante que altere manifestationes del morbo comencia presentar se. Es discutite le specificitate del test de lupus erythematose e le rolo del typo anaphylactoide de hypersensibilitate in le production de disseminate lupus erythematose.

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MYOCARDIAL INFARCTION IN WOMEN *

By THOMAS N. JAMES, M.D.,† HENRY W. POST, M.D., and F. JANNEY SMITH, M.D., F.A.C.P., *Detroit, Michigan*

EVEN more striking than the relative rarity of coronary thrombosis in women in the reproductive phase of life is the fact that thrombosis is seldom due to spontaneous arteriosclerosis. The unusual facets of myocardial infarction in women have evoked a number of interesting observations on the sexual aspects of this disease. Dock [1] demonstrated a remarkably thinner intima of the coronary arteries in females even in infancy. Wuest, Dry and Edwards [2] carefully examined the coronary arteries of bilaterally oophorectomized women and found they had a greater amount of atherosclerosis than a control group. Barr [3] was able to lower the cholesterol/phospholipid ratio in male survivors of myocardial infarction by giving them estrogens.

In previous publications many different features of myocardial infarction have been investigated, but most of these data were derived from series of both sexes,[4, 5, 6, 7] or of men only.[8, 9, 10] Two papers on the subject of this paper were published (1936 [11] and 1938 [12]) prior to the introduction of more accurate electrocardiography and prior to many recent discoveries regarding coronary artery disease and atherosclerosis, and their pathogenesis. Our study was undertaken in the hope that a modern analysis of myocardial infarction in women, plus a review of the present-day relevant literature, might provide some contribution to knowledge regarding the sexual disparity in this disease.

MATERIAL

One hundred forty-six women with myocardial infarction admitted consecutively from July, 1949, through July, 1953, comprise the substance of this study. The clinical diagnosis was accepted only if a typical series of electrocardiograms was associated with compatible clinical findings, and one or more of the following was present: fever, leukocytosis, neutrophilia, elevated erythrocytic sedimentation rate. A diagnosis on any other basis was accepted only if proved at autopsy.

RESULTS

General: The age range over which first myocardial infarctions occurred in these women was 27 to 81 years, and the average age at which the first infarct occurred was 64 years. The incidence of first infarctions by decades of life is illustrated in figure 1. The exact age of occurrence in one patient

* Received for publication January 14, 1955.
From the Division of Cardiology of the Henry Ford Hospital, Detroit, Michigan.
† Now on active duty with the United States Army.

was uncertain, so that only 145 patients are charted. There is a striking preponderance of cases in the sixth through the eighth decades. A more detailed breakdown by five-year periods revealed that only five women had their infarction before the age of 40, two more before the age of 45, then 11 in the 45 to 50 and 16 in the 50 to 55 age groups. The sharp upswing in incidence seems to be after 45. As will be noted later, 47.4 years was the average age at which 108 postmenopausal women in this series had reached the menopause.

At the time of this study 58 of the 146 patients were dead. Thirty-two (55.2%) of the 58 were autopsied. Thirty-six of these 58 died within the first year after their infarction, and almost equal numbers of patients (seven and eight) died each of the next two years. The longest survival among this group was 10 years. The number who died within the first year after

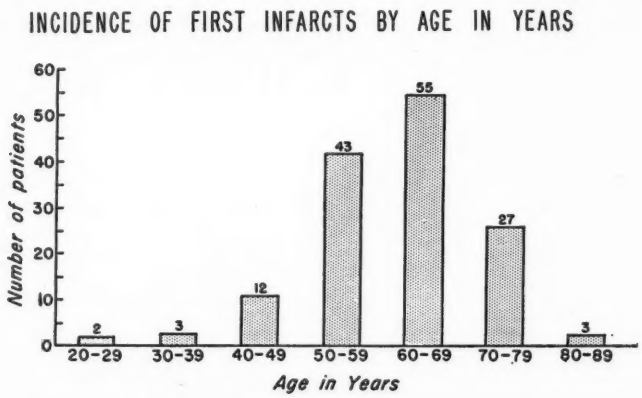

FIG. 1. The incidence of initial myocardial infarctions by age in years.

their initial infarction progressively increased with each decade. In women with their initial infarction in the 60 to 69 age group, 16 of the 20 dead at the time of this study died within the first year after infarction. Only general implications can be derived from these figures, since the majority of patients in this series of 146 are still living.

In 138 of the 146 patients the month in which the initial infarct occurred was known. There was no significant seasonal predominance, and the number per month for the 12 months, in sequence, was as follows: 14, 15, 13, 14, 7, 8, 16, 13, 12, 10, 8 and 8. The month of birth was known in 119 of the patients; that distribution in sequence was: 12, 10, 15, 12, 10, 10, 5, 10, 9, 7, 9 and 10.

The 58 deaths in this series included 45 (77.6%) who died from cardiac causes, eight (13.8%) who died from noncardiac causes, and five (8.6%) in whom the cause of death was unknown. Of the cardiac deaths, 28 died

within the acute phase (first month) after their initial infarction, 12 within the acute phase of a subsequent infarction, and five died of other cardiac causes (pulmonary edema, ventricular tachycardia) more than one month after evidence of an acute infarction. In the group of eight noncardiac deaths, four were due to cerebrovascular accidents, two to mesenteric thrombosis, and one each to Hodgkin's disease and suicide.

Incidence of Diabetes and Hypertension: These data are summarized in figure 2. As noted by others,[4, 6, 11] there is a high incidence of both diabetes and hypertension in women with myocardial infarction. The arbitrary level above which the blood pressure was judged to be hypertensive was 160/100 mm. Hg, as suggested by Glendy, Levine and White.[13] There was slightly

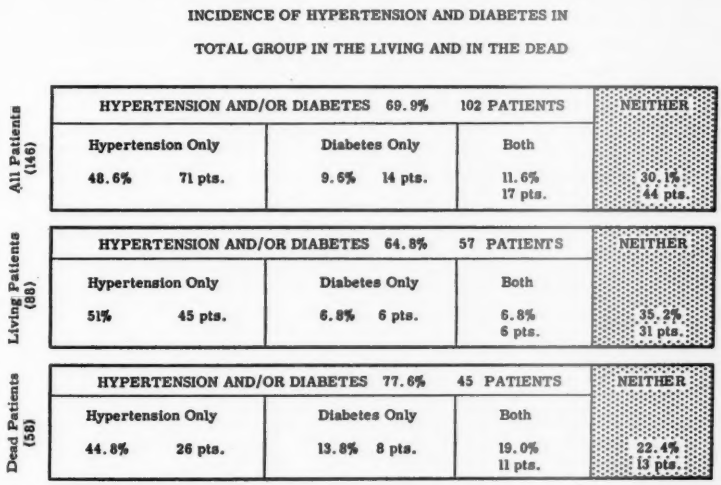

FIG. 2. A comparative graph of the incidence of hyperter.sion and/or diabetes in the entire group, the living patients and the fatal cases.

greater incidence of the two diseases in the dead patients than in the living ones.

Incidence of Obesity: Weights were recorded in 130 of the cases. Obesity was diagnosed if the patient weighed more than the maximal amount described for the given height of a person of large frame in standard life insurance tables. Eighty-four (64.6%) of the 130 were obese. Fifty-five (67.1%) of the 82 living patients who were weighed were obese. Twenty-nine (60.4%) of the 48 fatal cases whose weights had been recorded were obese.

Menstruation and Menopause: Date of the menopause was recorded in 108 patients. Eleven women were still menstruating at the time of their

infarction. Date of menarche was recorded in 61 patients, and averaged slightly over 14 years. A description of the menstrual cycle was present in 43 cases, of whom 39 had regular periods of normal duration and amount, one had regular periods with scant flow, two had irregular periods, and one had irregular periods plus a 10 year spontaneous amenorrhea. The number of pregnancies was recorded in 88 patients, and averaged 3.4 per patient. The number of deliveries was recorded in 122 cases, and averaged 2.6 per woman.

The average age at which menopause occurred in 108 of the women was 47.4 years. Since the average age of their initial infarction was 64.0 years, the average time between menopause and infarction in these 108 women was 16.6 years. Eleven of the remaining 38 women had had their initial infarction premenopausally. Unfortunately, the date of menopause was not recorded in 27 women, but the ages at which all 27 had their initial infarction was long after the period generally accepted for occurrence of the menopause.

Thirty-six patients had had pelvic surgery (oophorectomy, hysterectomy, perineorrhaphy, etc.). Only two women had had bilateral oophorectomy prior to menopause, their operations being at ages 40 and 42, and their myocardial infarctions occurred at 67 and 58, respectively.

Pilot Angina: A specific history as to whether angina pectoris had preceded the initial infarction was recorded in 119 patients. Of these, 48 (40.3%) had not had chest pain prior to the initial infarction. Of the 71 (59.7%) who had pilot angina, 16 had had pain for less than two months, eight for two to six months, nine for six to 12 months, and 24 had had pilot angina for over one year (over a range of 14 to 96 months, the average being 47 months). Fourteen women had had definite angina prior to their infarction, but were unable to tell exactly how long. No patient having an initial infarction after the menopause had angina prior to the menopause.

Pertinent Blood Findings: Hemoglobin determinations were made in 138 patients and averaged 13.2 gm./100 c.c. Red blood cell counts in 126 patients averaged 4.3 million/cu. mm. Hematocrit determinations in 115 patients averaged 45 mm. (Wintrobe). Leukocytosis and its neutrophilic partition varied from patient to patient but were essentially similar to previous reports;[4, 14] the same was true of the erythrocyte sedimentation rate.

Anticoagulants (Dicumarol and related antiprothrombin drugs) were administered to 99 (67.8%) of the 146 women. The contraindications, facility of control, dosage and complications were no different from those described by other authors.[15, 16]

There was only one patient with positive serologic tests for syphilis, but clinically she had no evidence of syphilitic cardiovascular involvement.

Social Habits: History regarding the use of alcohol and tobacco was available in 113 and 112 patients, respectively. Ninety women (80.3% of

the 112) did not smoke, 14 (12.5%) smoked less than one package of cigarettes per day, and seven (6.3%) smoked more than one package per day. One woman chewed tobacco.

Eighty-two (72.6% of 113) denied using any sort of alcoholic beverage. Twenty-eight (24.8%) drank moderately, and three (2.7%) drank excessively.

Precis of 11 Women with Initial Myocardial Infarction Prior to Menopause:

CASE REPORTS

Case 1. M. W. was born in 1912 and had her initial infarction in 1953. Her menses were regular, with menarche at age 15. She was gravida iii and para iii. Physical examination demonstrated hepatosplenomegaly and a blood pressure of 200/110 mm. Hg. A diagnosis of polycythemia rubra vera was established by a hemoglobin of 19.3 gm./100 c.c., a red blood cell count of 6.41 million/cu. mm., and a hematocrit of 74 mm. (Wintrobe). The blood viscosity (Ostwald) was more than 20 times normal, but serum viscosity was normal. Liver function tests and bone marrow aspiration were not remarkable. Blood cholesterol was 128 mg. %. Pilot angina was present for four months prior to the infarction, which was associated with classic Heberden pain, fever and an electrocardiogram indicating a posterior infarction. The patient was treated with phlebotomy, radioactive phosphorus and anticoagulants. Recovery was uneventful.

Case 2. L. R. was born in 1906, had her initial infarction in 1951, and died 13 days later. She had menstruated regularly until the time of her final admission. She was gravida v and para iv. A severe diabetic, she was also extremely obese. Blood pressure was ordinarily 124/60 mm. Hg, but she was in shock during most of her terminal illness. Blood cholesterol was 126 mg. %. Autopsy demonstrated severe coronary atherosclerosis, recent coronary thrombosis with myocardial infarction, and adenomyosis uteri.

Case 3. G. M. was born in 1900 and had infarctions once in 1945 and twice in 1953, the last two being six weeks apart. Her menopause occurred in 1952, prior to the last two infarctions. She was gravida vii and para v, and she had had toxemia of pregnancy in 1926. A diabetic since 1937, she was slightly obese and had a blood pressure of 200/100 mm. Hg. Autopsy after she died in the acute phase of the last infarction revealed myocardial fibrosis as well as a fresh anteroseptal infarction, a follicular cyst of the ovary, pulmonary fibrosis and encephalomalacia.

Case 4. C. F. was born in 1905 and had her initial infarction in 1952. At the time of infarction she was still menstruating regularly, but within the next year she began having menopausal symptoms. She was gravida ii and para ii. Moderately obese, she had a blood pressure of 180/104 mm. Hg. There was a strong family history of coronary arterial disease. The infarction was manifested by Heberden pain, fever and an electrocardiogram indicating posteroseptal infarction. Recovery was uneventful.

Case 5. G. N. was born in 1905 and had her initial infarction in 1952. She was still menstruating regularly at that time, but menopause occurred the next year. Blood pressure was 110/60 mm. Hg, and although not diabetic she was moderately obese. The infarction was manifested by Heberden pain, leukocytosis with neutrophilia, elevated erythrocyte sedimentation rate and an electrocardiogram indicating posterior infarction. Recovery was uneventful.

Case 6. D. M. was born in 1907 and had her initial infarction in 1951. At that time she was still menstruating regularly. She was gravida vii and para v. A

slightly obese chronic alcoholic, she was also a barbiturate habitué. Blood pressure was 180/110 mm. Hg, and she had mild hyperthyroidism, with a basal metabolic rate of plus 40. Blood cholesterol was 268 mg. %. Liver function tests were normal. Infarction was manifested by initial hypotension, Heberden pain, elevated erythrocyte sedimentation rate, leukocytosis with neutrophilia, and an electrocardiogram indicating anteroseptal infarction. Her recovery was uneventful.

Case 7. A. L. was born in 1901 and had her initial infarction in 1951. At that time she was still menstruating regularly, but menopause occurred the following year. She was gravida viii and para iv. Although not diabetic, she was obese and hypertensive (blood pressure, 190/110 mm. Hg). She was mildly anemic. Her infarction was manifested by Heberden pain, elevated erythrocyte sedimentation rate, leukocytosis with neutrophilia, and an electrocardiogram characteristic of posterior infarction. Recovery was uneventful.

Case 8. B. A. was born in 1918 and had her initial infarction in 1952. At that time she was still menstruating regularly. She was gravida i and para o, having had a therapeutic abortion in 1938 because of rheumatic heart disease with mitral stenosis. Blood pressure was 115/70 mm. Hg, and she had paroxysmal auricular fibrillation. While hospitalized for evaluation for mitral commissurotomy she had a coronary embolus, manifested by sudden Heberden pain, leukocytosis and electrocardiogram characteristic of posterior infarction. Her recovery was uneventful, and six months later she had a successful mitral commissurotomy.

Case 9. A. D. was born in 1914 and had her initial infarction in 1950. At that time she was still menstruating regularly. A severe diabetic for 12 years, she had been in diabetic acidosis and coma several times. She was gravida iii and para ii. She was normotensive (blood pressure, 140/90 mm. Hg) and of normal weight. Her course following the infarction was complicated by uremia, and she died one month after admission. Autopsy demonstrated acute myocardial infarction, intercapillary glomerulosclerosis and nephrosis.

Case 10. J. F. was born in 1923 and had her initial infarction in 1950. She was still menstruating regularly but had excruciating dysmenorrhea and had had a right oophorectomy. There was evidence of hypermetabolism, and the basal metabolic rate was plus 38. In addition, she had recurring syncope associated with severe abdominal pains. There was no history compatible with either rheumatic fever or congenital heart disease. Following her initial bout of severe Heberden pain she continued to have almost constant angina, requiring 30 to 60 nitroglycerin tablets daily. There was a loud systolic murmur and thrill in Roger's area. The electrocardiogram depicted an anterolateral myocardial infarction, and there was paradoxic pulsation at the apex of the left ventricle demonstrable both fluoroscopically and roentgenokymographically. Muscle biopsy on two occasions was normal. At the time of this study the chest pain was unimproved.

Case 11. L. P. was born in 1919 and had infarctions in 1952 and twice in 1953. She is still menstruating regularly. There was a past history of renal infection at the age of 16, and the patient was known to have been severely hypertensive since that time. Her blood pressure averaged 230/150 mm. Hg, but there was remarkably little change in the retinal arterioles. A thoracolumbar sympathectomy was done in 1945, at which time the adrenals were examined and found normal. There was no pharmacologic evidence of pheochromocytoma. Renal function tests were normal. She was neither diabetic nor obese, but had deep religious anxieties. A benign nontoxic thyroid adenoma was removed surgically eight weeks following the initial infarction. The infarctions were manifested by Heberden pain, leukocytosis with neutrophilia, fever, elevated erythrocyte sedimentation rate and electrocardiograms characteristic of anterior infarction. Recovery each time was uneventful except for a moderate amount of residual angina.

Comment: All of the above patients were premenopausal at the time of their initial infarction, although three (cases 4, 5 and 7) began to have menopausal symptoms approximately one year after the infarction. These three were all obese, and two of them were hypertensive. One of them (case 5) is the only patient of the 11 who was neither hypertensive nor diabetic, and presumably may have had her myocardial infarction on the basis of spontaneous coronary arteriosclerosis.

Of the other eight patients, three had myocardial infarctions secondary to systemic non-atherosclerotic diseases: case 1 had polycythemia rubra vera, case 8 had paroxysmal auricular fibrillation and rheumatic mitral valvulitis, and case 10 had some sort of systemic vascular disease which defied definition despite intensive study.

Four of the remaining five patients had extensive systemic arteriosclerosis, involvement of the coronary arteries being only one manifestation. Cases 2 and 9 were severely diabetic and difficult to control, case 3 had satisfactorily controlled diabetes but was hypertensive, and case 11 had had severe hypertension for 17 years.

The last of these 11 (case 6) had hypertension and hyperthyroidism, was moderately obese and consumed excessive amounts of alcohol and barbiturates.

In resumé it is well to reiterate that only one premenopausal woman (case 5) had a myocardial infarction presumably due to spontaneous coronary arteriosclerosis, without diabetes or hypertension (although she was moderately obese). This is an impressive contrast to the well recognized proclivity of coronary atherosclerosis for men in a comparable age group.

Discussion

The close association of coronary atherosclerosis and myocardial infarction, coupled with the observation that myocardial infarction is rare in premenopausal women, has prompted extensive consideration of the effects of estrogens on atherosclerosis. It has been demonstrated both [2, 17, 18] in man and in experimental animals [19, 20] that estrogens do affect cholesterol metabolism and thereby atherosclerosis.

Two divergent points which this trend of thought engenders, however, need to be reëxamined. First, coronary atherosclerosis and myocardial infarction, although closely associated, are not synonymous. (For example, 55% of the women in one series [8] had severe coronary sclerosis, but only 6% had clinical evidence of coronary artery disease.) Second, there are numerous effects of estrogens on blood vessels and the blood in addition to the effect on cholesterol metabolism (figure 3).

Relative to the first point, it does not seem sufficient to explain the infrequency of myocardial infarction in women before the fifth decade of life on the sole basis of their having less coronary sclerosis (figures 1 and 4). As illustration, one factor probably contributing to this sexual disparity is

a wider discrepancy in the amount of muscular activity, and consequently the amount of work for the heart, between the young man and young woman than between the two sexes in middle age. Partly because of this, the average female heart is smaller than the average male heart. Thus the male, born with a thicker coronary intima and lacking what antisclerotic protection estrogens may provide, has to supply blood for a larger mass of ventricular muscle which usually works harder than his sister's.

Relative to the second point, a thought-provoking study by Landesman and associates [21] on the blood vessels of the bulbar conjunctiva of normally menstruating women presented a number of pertinent observations. Vascular tone at the time of menstruation was noted to be altered considerably, and they state that the most striking and consistent of their findings was the

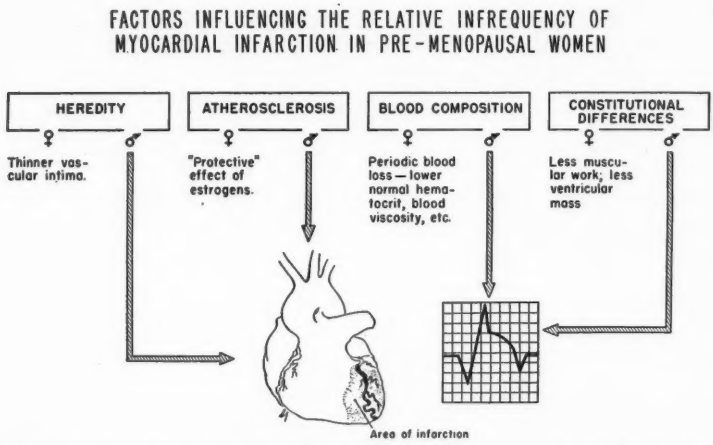

FIG. 3. A schematic representation of the effect on the blood vessels and the blood of hormones of the woman in the reproductive phase of life.

arteriolar dilatation during the week prior to menses. A corollary observation was an increased vascular sensitivity to topically applied epinephrine at the onset of menstruation. They suggest that premenstrual edema may be due partly to increased capillary permeability at the time of arteriolar dilatation. It would be interesting to speculate as to the long-range result these direct and indirect effects of estrogens would have on vascular physiology.

Although increased capillary permeability may be contributory, premenstrual hypervolemia and edema are due principally to the relationship of estrogens to sodium metabolism, either by a direct effect, or by an indirect effect through the adrenal cortex.[22] Another electrolyte affected by estrogens is calcium, which effect is the rationale for estrogen therapy of post-

menopausal and other types of osteoporosis. This effect on calcium is made more relevant by the recent demonstration by Uhl and associates [23] of some correlation between calcium and magnesium metabolism and atherosclerosis in experimental animals.

Aside from the hormonal changes during menstruation, the menstrual blood loss itself has a direct effect on the blood composition of women in the reproductive phase of life. Their average concentration of various blood constituents is less than that of males of comparable age, the relative red blood cell mass being a notable example. Some have felt that there are periodic alterations in the platelet count at the time of menstruation.[24] In addition, there is some evidence of an estrogenic effect on the control of hematopoiesis.[25] The difference in blood composition between women and

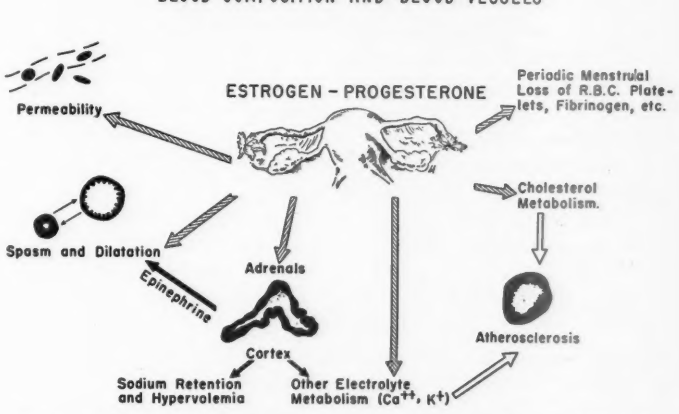

FIG. 4. A diagrammatic summary of factors influencing the sexual disparity of myocardial infarction.

men in the reproductive phase of life raises the question of whether there is an analogous difference in the facility with which a thrombus may occur in their coronary arteries.

Most studies on myocardial infarction or coronary disease in women have directed attention to the high incidence of hypertension and diabetes. Percentages have varied from 77 [12] to 92.2.[11] There seems to be little doubt that hypertension and diabetes are unusually frequent in women with myocardial infarction, but there has been an unfortunate swing of the pendulum to undue hesitation to diagnose coronary artery disease in the woman without hypertension or diabetes. Approximately 70% of our women with myocardial infarction had one or both of these diseases, but the fact that

30% did not should not be overlooked. A more specific use of this axiom could refer to the premenopausal woman. Over 90% of our premenopausal women had either hypertension or diabetes, or both.

There was no correlation between the use of tobacco or alcohol and the occurrence of myocardial infarction in these women, although there were relatively few users of either. A smaller percentage of our patients was obese (64.6%) than some have reported.[12] Approximately the same percentage was obese among the living as among the dead.

Characteristics of the menses, fertility and childbearing of the patients in our series differed in no significant respect from those of women who do not develop myocardial infarction. This evidence suggests that there is no prevalence of hypoestrogenic females among those who subsequently have coronary artery disease.

Sixteen years, the length of time between the average age of menopause and occurrence of initial infarction, is long enough for a considerable amount of coronary atherosclerosis to develop after the cessation of ovarian function, if it is to be presumed that the functioning ovaries have held it in abeyance until then. However, the degree of coronary atherosclerosis apparently exhibits a gradual progressive increase from the age of 30 to 75,[26] and there is no sharp upswing postmenopausally. Is this gradual increase in atherosclerosis sufficient to account for the sharp upswing in incidence of myocardial infarction postmenopausally (figure 1)? Possibly some of the other effects of estrogens (figure 3) are more sorely missed after the cessation of ovarian function than the effect on cholesterol metabolism, and presumably atherosclerosis.

Although the average degree of coronary atherosclerosis in women at the age of 64 (average age of initial infarction in our series) is still significantly less than that of men of the same age,[10, 26] the incidence of myocardial infarction in the two sexes at this age is very similar.[27]

Summary and Conclusions

1. This is a review of 146 cases of women with myocardial infarction.

2. The average age of menopause was 47.4 years, and the average age of initial infarction was 16.6 years later.

3. There is a sharp rise in incidence of myocardial infarction after the fifth decade of life in this series. This is difficult to account for solely on the basis of a gradual increase of atherosclerosis during this period.

4. Hypertension and/or diabetes was present in 69.9% of the entire series, 63.6% of the living patients, 77.6% of the fatal cases, and 90.9% of the premenopausal group.

5. Of the 11 women who had their initial infarction prior to menopause, only one failed to have an accompanying condition that could conceivably have contributed to atherosclerosis.

6. In addition to the well recognized effect of estrogens on cholesterol metabolism and experimental atherosclerosis, there are other important effects of estrogens on the blood vessels and the blood. Some of these are discussed.

7. Factors contributing to the relative immunity of premenopausal women to myocardial infarction are reviewed.

Summario in Interlingua

Le disparitate sexual inter le frequentia de infarcimento myocardiac in homines e in feminas es ben recognoscite. Iste reporto se basa super un studio del serie consecutive de 146 feminas con infarctos myocardiac qui esseva admittite a nostre hospital ab le comenciamento de julio 1949 usque al fin de julio 1953.

Le limites de etate inter le quales prime infarcimentos habeva occurrite esseva 27 e 81 annos. Le etate median esseva 64 annos. Le plus alte frequentia se concentrava in le sexte, septe, e octave decades del vita. Le serie includeva 5 casos de patientes sub 40 annos de etate, 2 inter 40 e 44, 11 ab 45 a 49, e 16 ab 50 usque al fin de 55. Le augmento de frequentia occurreva post le etate de 45 annos.

Hypertension e/o diabete mellite esseva presente in 69,9 pro cento del serie integre, in 63,6 pro cento del patientes vivente, in 77,6 pro cento del casos mortal, e in 90,9 pro cento del casos premenopausic.

Infarcimento myocardiac occurreva in 11 feminas qui menstruava ancora. Le etate median de 61 feminas al tempore de lor prime menstruation habeva essite pauco minus que 14 annos; 108 del feminas habeva habite lor menopause a un etate median de 47,4 annos. Le intervallo median inter menopause e infarcimento myocardiac initial esseva 16,6 annos.

In le gruppo del 11 feminas qui habeva infarctos myocardiac ante le menopause, omnes excepte una habeva alicun morbo subjacente. Iste morbo esseva hypertension, diabete mellite, polycythemia rubie ver, morbo cardiac rheumatic con stenosis mitral, o hyperthyroidismo. In plure casos iste morbos occurreva in combination.

Il ha plure punctos digne de mention in re le disparitate sexual in infarcimento myocardiac. Es a considerar le effecto de estrogeno super le metabolismo de cholesterol e etiam super le metabolismo de natrium, calcium, e possibilemente magnesium. Altere factores importante es le perdita de constituentes sanguinee durante le menstruation e le grado generalmente inferior de activitate muscular in feminas in comparation con homines, lo que resulta in minus labor cardiac.

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CEREBRAL COMPLICATIONS OF HYPOTENSION*

By Joseph F. Fazekas, M.D., Jack Kleh, M.D., and Alvin E. Parrish, M.D., *Washington, D. C.*

Reversible functional disturbances, localized infarctions and permanent loss of function of the higher centers are complications that may result from varying degrees of cerebral vascular insufficiency induced by hypotension. Cerebral arteriosclerosis may also predispose to similar disturbances. This is understandable since in both conditions the rate of cerebral blood flow may be reduced to values below that compatible with normal cellular activity. When hypotension and cerebral vascular disease coexist, cerebral complications are more likely to occur, since their effects may be additive. Since it is practically impossible to determine the extent of cerebral arteriosclerosis, it can be anticipated that with the use of potent hypotensive agents the incidence of cerebral complications may increase, even in those subjects whose blood pressure can be maintained within normal limits.

In this report, observations of disturbances induced by varying degrees of hypotension are presented.

Pathologic Physiology of Cerebral Vascular Insufficiency

The delivery of substrates essential for the metabolic activity of various organs is the primary function of the circulatory system, those cells with the highest metabolic demands requiring the largest supply of blood. The adult brain, which weighs about 1,400 gm., receives about 800 c.c. of blood and utilizes approximately 50 c.c. of oxygen each minute. The magnitude of the oxygen and blood flow demands of the brain becomes apparent when it is realized that it requires about one fifth of the total oxygen consumption and cardiac output of an average sized man.

The rate of blood flow to the brain is dependent principally upon the arterial pressure and the vascular resistance, the latter representing the frictional opposition to the flow of blood, and is influenced by alterations in the diameter of the vessel and by the viscosity of the blood. A significant reduction of pressure or increase in vascular resistance will result in a diminution in the rate of blood flow. Under normal conditions, with a moderate reduction of pressure, the rate of blood flow to the brain may be maintained within normal limits by vascular dilatation.[1] Compensation may also be achieved by a greater extraction of essential substrates from a slowed cir-

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From the George Washington and Georgetown University Medical Divisions, District of Columbia General Hospital, Washington, D. C.

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culation, the metabolic rate of the organ being thus maintained within normal limits.[2] There is, however, a critical rate of blood flow below which these mechanisms can no longer compensate for the reduction in blood pressure, the delivery of essential substrates becomes inadequate, and the cerebral metabolic rate decreases.[2] The immediate alterations in functional activity resulting from a reduction in the rate of blood flow below critical values are most likely due to an inadequate oxygen delivery.

The only way the brain or any other organ can tolerate a rate of blood flow below critical values is by a reduction of its energy requirements. This is probably the explanation for the observation that a lowering of the basal metabolic rate is effective in alleviating certain cases of coronary insufficiency, and that the hypothermic brain can tolerate a greatly decreased rate of flow. Drugs such as barbiturates, when given in concentrations which depress oxidative processes, may also protect against a reduced delivery of essential substrates.

Under normal conditions the amount of blood flowing to the brain is more than sufficient for its metabolic activity. The rate of cerebral blood flow for young normal adults is about 55 c.c./100 gm. of brain/min.[3] This value may be reduced acutely to approximately 30 c.c./100 gm./min. before manifestations of cerebral vascular insufficiency become evident.[2] The excess flow probably permits safe and rapid circulatory adjustments to reflex alterations in the distribution of blood such as occur with postural adjustments or temperature changes.

The presence of vascular disease will not influence the blood flow requirements of an organ, since it does not directly alter the energy requirements of the cells. An increase in vascular resistance resulting from hypertension, atherosclerosis, or both, may impede the flow of blood to such an extent that vascular reserves are so depleted that the delivery of essential substrates is barely sufficient to meet the metabolic demands of the cells. This situation is encountered in patients with angina of effort, but may occur with advanced cerebral vascular disease. In such instances a further decrease in the rate of blood flow or an increase of its metabolic requirements cannot be compensated for, and cellular insufficiency results.

Under normal conditions the brain is perhaps the organ most sensitive to an acute reduction of blood pressure, since manifestations of cerebral vascular insufficiency are usually observed before signs of myocardial, renal or hepatic vascular insufficiency become evident.[2] The consequences of a reduction in the rate of cerebral blood flow below critical values will be determined by the duration of the cerebral ischemia and the area of the brain most affected. With a normal cerebral vascular tree, those cerebral cells with the highest metabolic demands will be the first to suffer from ischemia. A relatively brief period of cerebral ischemia will result in reversible functional disturbances, whereas with prolonged periods of energy deprivation the brain will be irreversibly damaged.

Cerebral Disturbances

I. *Reversible Functional Disturbances:* Reversible functional disturbances were induced in a number of subjects by acutely reducing the mean arterial pressure by the intravenous administration of either hexamethonium chloride or Arfonad.* Blood pressure was recorded directly from the femoral artery with a damped aneroid manometer.[4] The subjects were usually maintained at a 20° tilt (head up) while receiving the drugs. The mean arterial pressure was reduced to critical levels within two to 10 minutes.

The manifestations of cerebral ischemia most frequently observed were sighing, yawning, confusion, staring, convulsions and loss of consciousness. The subjects usually became extremely apprehensive and restless and complained of "dizziness" before the blood pressure reached critical values. Consciousness was immediately restored by discontinuing administration of the hypotensive agent and tilting the subject to the head-down position. Confusion and lethargy persisted, however, sometimes for as long as 20 minutes after restoration of consciousness.

Table 1

Acute Hypotension and Cerebral Vascular Insufficiency

Condition	Age Range	No. of Subjects	Mean Art. Pressure (mm. Hg)				Cerebral Vascular Insufficiency
			Control		Experimental		
			Range	Mean	Range	Mean	
Normal	30–46	7	75– 94	84	29– 44	35	Yes
Essential hypertension	53–71	9	110–192	148	64–124	78	Yes
Essential hypertension	48–66	3	102–180	140	52– 79	65	No
Malignant hypertension	21–47	11	125–215	180	76–126	103	Yes
Malignant hypertension	34–43	4	160–204	188	88–100	96	No
Hypertensive cerebral vascular disease	50–76	10	110–200	143	50–135	71	Yes
Hypertensive cerebral vascular disease	59–80	2	122–158	140	30– 30	30	No

The mean arterial pressure at which signs of cerebral vascular insufficiency became manifest varied considerably, as indicated in table 1.

Hypotensive crises with postural changes are not uncommon in subjects receiving potent ganglionic blocking agents. In such instances the acute reduction of pressure below critical values results from a suppression of vasoconstrictor reflexes.

The following observations were made on a 34 year old woman with

* d-3,4(1′,3′-dibenzyl-2′-keto-imidazolido)-1,2-trimethylene thiophanium d-camphorsulfonate.

malignant hypertension. Her pressure prior to drug therapy (Ansolysen) was 250/155 mm. Hg and was not appreciably influenced by the drug until she was receiving 130 mg. three times a day. Because of a syncopal attack, the dose was reduced to 110 mg. three times a day. At this concentration her blood pressure returned to the original values. Hypotensive crises nevertheless continued to occur with changes in position, and it was necessary to discontinue drug therapy. Prior to the discontinuance of the drug the mean arterial pressure and cerebral hemodynamics were determined with the patient in various positions. The findings in table 2 demonstrate the development of cerebral vascular insufficiency at a relatively high pressure on assuming the upright position.

These data suggest that subjects with cerebral vascular disease in many instances are unable to compensate for rapid reductions of pressure and develop signs of cerebral vascular insufficiency at higher pressure levels than do normal young subjects. Apparently in such cases the increased vascular resistance secondary to hypertension and vascular damage cannot be readily

TABLE 2

Cerebral Hemodynamics during Postural Hypotension

Position	Time a.m.	MAP	CBF	$CAVO_2$	Signs and Symptoms of C.V.I.
Horizontal	10:32	178	64.4	3.55	None
Sitting	10:37	120	43.2*	5.33	Lightheaded and nauseated
Standing	10:38	80	36.0*	6.39	Convulsions and unconsciousness
Horizontal	10:42	160	69.9*	3.29	Apathetic

* Calculated assuming constant cerebral oxygen consumption of 2.2 c.c./100 gm./min.

In this table, MAP signifies mean arterial blood pressure in mm. of Hg; CBF, cerebral blood flow in c.c./100 gm. of brain/min.; $CAVO_2$, cerebral arteriovenous oxygen difference in vol. %; and C.V.I., cerebral vascular insufficiency.

overcome, so that even at approximately normal pressure levels the amount of blood delivered to the brain may be inadequate to meet the metabolic demands of certain cerebral cells.

II. *Cerebral Infarction:* Cerebral infarction is a not infrequent complication in subjects receiving potent hypotensive agents. Unfortunately, in many instances the exact nature of the accident is undetermined. In Smirk's series of patients receiving hypotensive drugs he noted that "those who died did so mainly through stroke and were active up to the time of the cerebral accident." [5]

In patients with hypertensive cerebral vascular disease the area of the brain most susceptible to ischemia is probably that supplied by the vessel whose lumen is most constricted by the disease process. With a decrease in pressure and a concomitant reduction in the rate of cerebral blood flow in an already compromised cerebral circulation, a favorable environment for the formation of cerebral thrombosis is established. However, more likely than thrombosis is the possibility of ischemic cerebral infarction. The high

incidence of fatal cerebral infarctions for which evidence of mechanical occlusion is lacking has been demonstrated by Hicks and Warren.[6] More recently Denny-Brown [7] and Putnam [8] have reported the occurrence of transient and permanent focal signs associated with reductions of pressure in patients with narrowing of their cerebral vessels. In their study, etiologic factors were gastrointestinal hemorrhage, myocardial infarction associated with shock, hypotensive agents and postural hypotension.

Our experience with both acute and prolonged administration of hexamethonium to subjects with hypertensive cerebral arteriosclerotic syndrome also demonstrates the hazards associated with a reduction of pressure in such subjects. Upon acute administration of hexamethonium chloride (intravenously, 1 c.c. of 2% solution per minute) to nine subjects, signs of cerebral vascular insufficiency were observed with a reduction of the mean arterial pressure from 161 to 82 mm. of Hg, the rate of cerebral blood flow falling from 39 to 25 c.c./100 gm. of brain/min. With a gradual reduction of pressure achieved by subcutaneous administration of hexamethonium chloride to the same group of subjects, the mean arterial pressure was reduced to a mean of 98 mm. of Hg. With the gradual reduction of pressure there was no change in the rate of total cerebral blood flow from control values. Four of the nine subjects nevertheless exhibited manifestations of increased cerebral vascular insufficiency, characterized by lethargy, somnolence and increased confusion. Withdrawal of the drug was followed by improvement in mental status. One subject, the youngest of the group, sustained a cerebral vascular accident and succumbed.

The following case demonstrates the difficulty encountered in differentiating the effects of hypotension from those of progressive vascular disease.

Case Report

The patient, a 65 year old woman, was admitted to the hospital because of hypertension (blood pressure, 240/116 mm. Hg) and recurring attacks of middle cerebral artery insufficiency characterized by transient aphasia, paresthesias and weakness of the right extremity. Ansolysen (40 mg. three times a day) was prescribed, along with bed-rest and a low salt diet. The day following admission the patient was free of complaints and was permitted to sit in a chair. Within a few minutes she was sweating profusely, her skin was cold and clammy, her pulse was rapid, and she became unconscious. On her regaining consciousness (period of unconsciousness estimated to be about 10 minutes), examination disclosed signs of complete middle cerebral artery occlusion, and the patient was apathetic. The dose of the hypotensive agent was reduced to 20 mg. three times a day. The following day her condition remained essentially the same, and cerebral metabolic studies were undertaken with the patient in the horizontal position. Shortly after the studies were completed (30 minutes), it was noted that the patient was sweating profusely and that her mean arterial pressure had fallen from 115 to 52 mm. of Hg. The table was immediately tilted to a head-down position, and the pressure returned to control values within five minutes. Fifteen minutes later she was tilted head up 15 degrees, and within two minutes her mean arterial pressure fell from 104 to 50 mm. of Hg. She was again tilted to the head-down position, and her pressure returned quickly to control values.

She was kept in the head-down position for the next 24 hours, and hypotensive therapy was discontinued. The patient remained listless, apathetic and aphasic, and the motor paralysis showed no evidence of lessening one week after her initial syncopal attack.

When the patient's mean arterial pressure was 115 mm. Hg, her rate of cerebral blood flow was 34.0 c.c./100 gm. of brain/min., and the cerebral metabolic rate was 2.6 c.c./100 gm./min. These values are significantly reduced from values obtained in normal young subjects, and are consistent with those observed in subjects with advanced cerebral vascular disease. The cerebral arteriovenous oxygen difference at the time her mean arterial pressure was 50 mm. Hg was 9.7 vol. %. Assuming a constant cerebral metabolic rate, the calculated rate of cerebral blood flow at this pressure was 26.6 c.c./100 gm. of brain/min., a value significantly below the previously determined critical rate of cerebral blood flow. An electroencephalogram obtained several days after the hypotensive agent was discontinued disclosed a diffuse slow wave pattern consistent with generalized brain damage.

It is difficult to determine if the infarction of the area supplied by the middle cerebral artery resulted from progression or extension of a thrombus or from ischemia secondary to the hypotension. The chain of circumstances strongly suggests the latter possibility. The development of a hypotensive crisis with the patient in the horizontal position and with only a 15 degree head-up tilt further emphasizes the hazards attendant upon the use of potent hypotensive agents, particularly in subjects with cerebral vascular disease.

A possible explanation for the increased manifestations of cerebral vascular insufficiency in the above cases is a disproportionate distribution of the available blood within the cerebral vessels. This is probably due to failure of relaxation of the more arteriosclerotic cerebral vessels and a proportionately greater dilatation of those less damaged in response to a gradual reduction of the mean arterial pressure. Thus, an appreciable amount of the available blood may be shunted under such circumstances from those areas of the brain with the least vascular reserve.

III. *Shock:* The alterations of cerebral hemodynamics and metabolism resulting from sustained hypotension are not too well understood. It is inevitable, however, that an organ so dependent on its circulation will be adversely affected if the arterial pressure and its blood flow are permitted to fall below critical values for even a short period of time. It is generally recognized that, during shock, reflex vasoconstrictor mechanisms are activated which shunt blood away from relatively unimportant viscera such as muscle, kidneys and liver to the more vital organs, the brain and heart. Early in shock there may be a significant reduction in total cerebral blood flow,[9] but the brain is nevertheless capable of extracting from the slowed circulation sufficient substrates to maintain its metabolic rate within normal limits. This is evidenced by the significantly increased cerebral arteriovenous oxygen difference noted in such instances, and by the clinically well recognized fact that patients may be conscious despite an unobtainable blood pressure. The decreased cerebral arteriovenous differences and lowered cerebral metabolic rate noted in patients who have been in shock for some time may reflect cerebral damage resulting from a failure of compensatory

mechanisms. The possibility arises that irreversible shock may in part result from a reduction in the rate of cerebral blood flow below critical values for a period of time sufficiently prolonged that cerebral cells cannot recover from their energy deprivation, even though an adequate cerebral circulation may subsequently be effected.

The possibility arises that irreversible shock is more likely to develop from hypotensive episodes in subjects who are under the influence of ganglionic blocking agents. Such agents, because of their pharmacologic action, may suppress compensatory reflex mechanisms which serve to protect the vital organs when they are threatened by an acute reduction of pressure. It may indeed be fortunate that syncope results in a loss of postural reflexes, since the horizontal position assures a more adequate cerebral circulation.

IV. *Irreversible Brain Damage:* Perhaps the most dramatic illustration of the importance of a sufficient pressure head to drive blood through the cerebral vessels is seen in subjects who survive after a period of cardiac arrest. The following case demonstrates the extreme vulnerability of the cerebral cells to ischemia. The patient developed cardiac arrest immediately following the anesthetization of the larynx with procaine. Within a period of less than 10 minutes heart action was restored and the blood pressure was within normal limits. It is now more than three years since the incident occurred. The patient has never regained consciousness and exhibits findings characteristic of decerebrate rigidity. Vital signs are normal, and there is no evidence of myocardial, renal or hepatic dysfunction.

V. *Retinal Damage:* Since the circulation to the eye is dependent on an adequate cerebral circulation, the possibility arises that retinal vascular insufficiency may also result from hypotension. The metabolism of retinal tissue parallels to a great extent that of the brain. Both organs are dependent on glucose as their principal source of energy. The in vitro oxygen consumption of the retina is higher than that of brain tissue, as is its rate of both aerobic and anaerobic glycolysis.[10] The sensitivity of the globe and the visual pathways to ischemia has been demonstrated experimentally by Weinberger.[11] Ophthalmoscopic examination of the subject with irreversible brain damage disclosed bilateral temporal disc pallor which suggests a papillomacular bundle defect. Amblyopia which persisted for as long as 15 minutes was noted in three of our subjects in whom the mean arterial pressure was acutely reduced to critical values. This may well have been due to retinal ischemia secondary to the hypotension.

Summary

The cerebral complications that result from spontaneous or induced hypotension include reversible functional disturbances, localized infarctions, and permanent loss of function of the higher cerebral centers. The mean arterial pressure at which signs of cerebral vascular insufficiency become manifest varies considerably and is frequently highest in those subjects with cerebral

vascular disease. In patients receiving hypotensive agents it may be difficult to determine if the cerebral complication arises from a progression of the vascular disease or from hypotension, since in both situations the delivery of essential substrates becomes inadequate.

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SUMMARIO IN INTERLINGUA

Le complicationes cerebral que pote resultar de hypotension (o spontanee o inducite), include revertibile disturbationes functional, infarcimentos localisate, e dysfunctionamento permanente del centros cerebral superior. Le consequentias que resulta quando le fluxo sanguinee del cerebro es reducite a infra valores critic, es determinate per le duration del ischemia cerebral e le extension del area in que le systema nervose central es primarimente afficite. Le pression arterial median con que signos de insufficientia cerebro-vascular comencia manifestar se es multo variabile e frequentemente attinge valores maximal in individuos con morbo cerebro-vascular. In tal casos le vasos cerebral non ha le capacitate a relaxar se sufficientemente pro compensar le acute reduction pressional.

Proque il non es possibile determinar quantitativemente le grado del morbo cerebro-vascular in le caso individual, il seque que le reduction therapeutic del pression sanguinee—si e quando illo es indicate—debe esser inducite gradualmente e per medio de agentes que non causa abrupte alterationes pressional.

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AN EPIDEMIC OF HISTOPLASMOSIS INVOLVING MAN AND ANIMALS*

By M. L. FURCOLOW, M.D., *Kansas City, Kansas,* R. W. MENGES, D.V.M., *Chamblee, Georgia,* and H. W. LARSH, Ph.D., *Kansas City, Kansas*

ALTHOUGH the characteristics of 13 epidemics of histoplasmosis have been described by Furcolow and Grayston,[1, 2] the present epidemic represents one in which complete studies were done not only of the human cases but also of the animals and, in particular, the environment from which the infection was acquired. From the site of this epidemic the first isolation of *Histoplasma capsulatum* from the air was made.[3]

This epidemic occurred on a farm near Atcheson, Kansas, and involved a mother, father, their two sons, and the brother of the father. The medical histories of each case will be described and x-rays will be shown of the various cases.

On July 1, 1952, the father (J. E. T.) purchased a farm which had been idle for the two previous years, to which the family moved about August 15. They spent the first few days cleaning about the house, and on Friday, August 22, cleaned the chicken coop, which had not been used for two years (figure 1). The debris on the dirt floor, described as being from 4 to 8 inches deep, was shoveled into a manure spreader to the accompaniment of considerable dust. The spreader was filled three times in all. The first load was filled by the brother of the owner (A. H. T.), who also shoveled the remainder of the material into the doorway in a pile. The second filling of the manure spreader was done by the mother and the two children on Saturday, August 23, and the third load was filled on Sunday, August 24, by the father. The material from the chicken house was spread on nearby fields. On Saturday, August 30, eight days after the first cleaning of the chicken house, the entire family fell ill as follows:

Walter Lee, age three, became ill with dry cough, fever, restlessness, loss of appetite and headache. Fever was reported as high as 106° F. His fever lasted one week and he was in bed for two weeks. When first seen, 75 days after onset, his sedimentation rate was 12 mm. in one hour. This subsequently dropped below 10 mm. Skin tests at this time were negative to tuberculin and positive to histoplasmin. Serologic studies showed positive complement fixation test for histoplasmosis. These tests have subsequently become negative. Chest x-ray of November 13 (75 days after onset) still showed definite perihilar infiltration on both sides, with considerable granularity throughout both lung fields (figure 2). Follow-up x-ray of March 10, 1954, showed definite evidence of calcification developing (figure 3).

James R., age six, had fever, headache, restlessness, loss of appetite and some difficulty in breathing. The temperature rose to above 103° F. His fever lasted

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approximately one week, but he was confined to bed for about two weeks. His sedimentation rate 75 days after onset was 15 mm. in one hour. This subsequently dropped to 5 mm. in one hour. At this time he gave negative tuberculin and positive histoplasmin skin tests. Chest x-ray on November 13 (75 days after onset) showed disseminated nodular infiltrations in both lung fields with enlarged hilar node (figure 4). Follow-up x-ray on March 10, 1954, still showed generalized granularity with enlarged right hilar lymph nodes. Serologic tests for histoplasmosis were positive when the patient was first seen, 75 days after onset, but later became negative.

Opal G., the mother, age 27, had chills, fever and headache. She had malaise for two or three weeks but did not stay in bed. Her sedimentation rate when first seen, 75 days after onset, was 5 mm. in one hour. Her tuberculin and histoplasmin

FIG. 1. Chicken coop which shows source of epidemic of histoplasmosis.

skin tests were positive at this time. Serologic tests for histoplasmosis have been doubtful or positive on each of four occasions, the last on March 10, 1954. Her first chest x-ray, on November 13 (75 days after onset), showed calcified lesions in the right apical and hilar areas. There was a small nodular infiltrate in the left fifth and sixth interspaces. The deposition of calcium in this lesion was evident on the last film, on March 10, 1954. None of these x-rays was considered satisfactory for reproduction.

James E., the father, age 30, had headache and a chilly sensation, and felt as though he was coming down with influenza. His temperature lasted only one day. The degree of fever is not known. He felt ill for two or three days but did not go to bed. His sedimentation rate when he was first seen was normal. Skin tests, 75 days after onset, were negative to tuberculin and positive to histoplasmin. The first chest

x-ray, on November 13 (75 days after onset), showed granular infiltration throughout both lungs. There was a definite lesion in the right fifth interspace, with large hilar lymph nodes on the right. The last chest x-ray, on March 10, 1954, showed the lesion in the right fifth interspace to be calcifying. The hilar lymph nodes on the left still appeared enlarged. There was still considerable granularity throughout the lung fields. None of these x-rays was considered satisfactory for reproduction. Serologic tests for histoplasmosis were positive on three occasions and doubtful on the last test, in March, 1954.

Alfred H., age 16, the brother of the family head, had been living with the family for five years. His illness began on August 30, 1952. He had a severe headache, cough, loss of appetite and a fever. He remained at home unable to attend school on

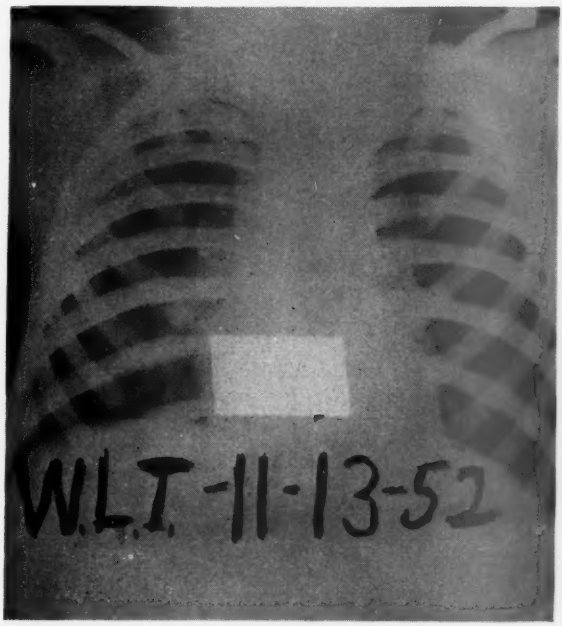

FIG. 2.

the following Monday, three days after onset. On the fourth day he felt somewhat better and went to school but still did not feel at all well. He still had headaches and dizziness. He continued to attend school until the sixth day after onset. On that date he came home feeling too ill to continue. He had fever, headache and pain in the stomach, and this continued through the next day. He was seen by a physician who thought that he had "old fashioned flu." He was given castor oil and pills and remained in bed from Friday until the following Tuesday (September 8, nine days after onset). On that date, still not feeling well, he again saw his local physician. He returned to the physician's office the following day and was sent to the hospital. At this time the diagnosis of possible appendicitis was entertained, but following a chest x-ray he was told he had extensive bronchial pneumonia. He continued to feel

bad and was treated with various antibiotics, but failed to improve. It was thought at that time that he might have tuberculosis, but a tuberculin test was found to be negative. On Monday, September 22 (23 days after onset), the patient was transferred to another hospital, where tests with tuberculin again were negative. Sputum tests were also negative for acid-fast bacilli. A histoplasmin skin test was found to be positive, and the serologic test for histoplasmosis was strongly positive (1:32). The first serologic test was drawn September 29 (30 days after onset). The boy remained in this hospital for 47 days and continued to have fever, elevated sedimentation rate and cough with slight sputum. His symptoms gradually subsided, although he still felt weak on discharge from the hospital, 70 days after onset of his illness. Laboratory tests during hospitalization showed normal urinary findings. His red

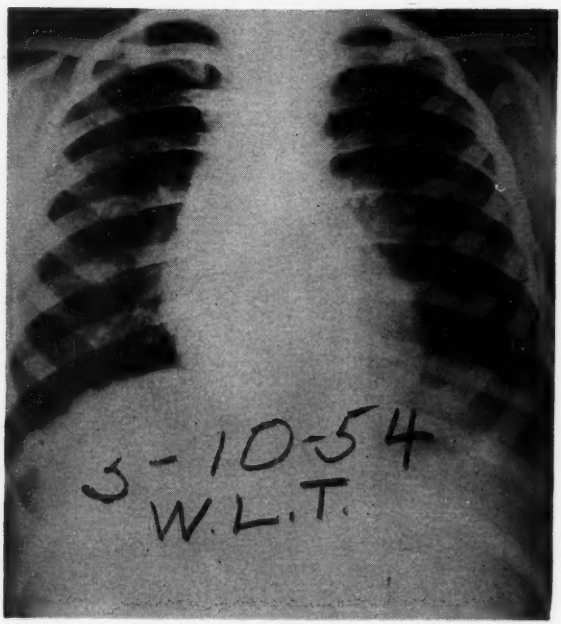

FIG. 3.

blood cell count was 4,900,000; hemoglobin, 85%; white blood count, 6,100. The Klein test was negative. Sputum examinations for tubercle bacilli were negative. Sedimentation rate of 24 mm. on September 23 subsequently fell to 18 mm., then to 14 mm. in one hour at time of discharge. It was still 11 mm. on November 13 (75 days after onset). Subsequent tests were normal. Skin tests, 75 days after onset, showed the tuberculin, blastomycin and coccidioidin tests to be negative, and the histoplasmin to be positive. Serologic tests at this time were unchanged from those made 45 days previously. Subsequent serologic tests have shown a slow fall toward normal, although the precipitin and complement fixation tests were still positive on March 8, 1954. X-rays taken on September 11, 1952, revealed marked, generalized snowflake appearance throughout both lung fields. Both hilar lymph nodes appeared

enlarged (figure 5). Subsequent x-rays have shown a slow clearing of the process, although the last x-ray, taken on March 8, 1954, approximately one and one-half years after onset, still shows a faint granularity. The left hilar lymph nodes still appear to be enlarged. There is a question as to whether calcification is developing.

Although the results of the different serologic tests on various members of the family are somewhat irregular, all members of the family had a positive serologic test at some time or other. At the time of the last tests, some 557 days after onset of illness, two of the family showed doubtful serologic tests, and the most severely infected patient still showed a positive test.*

FIG. 4.

Four samples of soil were collected on November 13, 1952, from the farm: one from the chicken house, one from outside the chicken house door, a random sample from along a garden fence, and another from the wheat field north of the house where the chicken droppings had been spread. Of these, the sample taken from the chicken house was positive for *H. capsulatum*. At the second collection, on December 9, 1952, 10 samples were taken

* The authors express their appreciation to Dr. Joseph Schubert, of the CDC Serological Laboratories, USPHS, and to Dr. Samuel Salvin, of the Rocky Mountain Laboratory, USPHS, for preparing the serologic tests.

as follows: from a chicken manure pile in barn, from old wallpaper and plaster cleaned out of house, from around the outside of the main barn, outside door of chicken house, inside chicken coop on floor (two samples), outside small garage, from open field where chicken manure was dumped, from around foundation of house and woodpile, and from pigeon manure from barn. Of these, two were positive, one from inside the chicken house, as before, and the other from just outside the door of the chicken house in an area where the material had been dumped in the process of cleaning the chicken house.

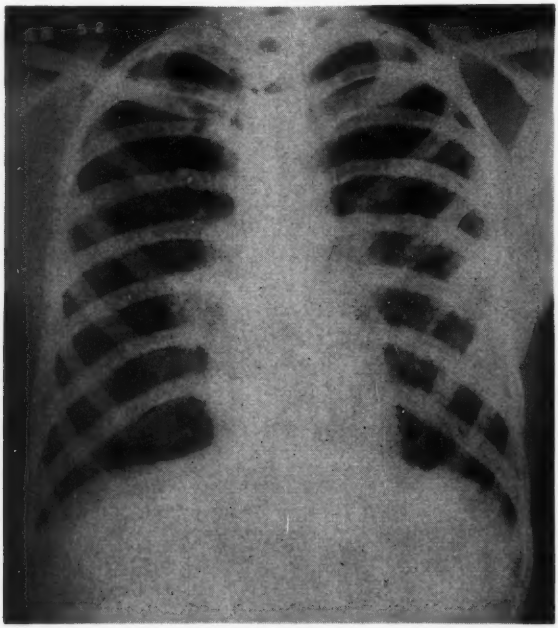

FIG. 5.

It is interesting to note that the wife's father and mother lived with the family. Neither took part in the cleaning of the chicken house, and neither showed any signs of illness. Skin tests performed on the mother, Mrs. E. B., age 45, were positive to tuberculin and negative to histoplasmin, blastomycin and coccidioidin. Both chest x-ray and serologic tests for histoplasmosis were negative.

Animal Studies: Histoplasmin skin tests were carried out on a number of the farm animals which were in contact with the residents of the farm. Two of three cattle were found to be reactors to the skin test. One of 27

chickens was found to be positive when skin-tested but cultures at autopsy were negative. Of the 11 dogs present on the premises, all of which played in the neighborhood of the chicken house, four had positive skin tests and five had positive cultures. Skin tests and cultures of three kittens were negative, but one older cat had a positive culture for *H. capsulatum.*

In addition to the above animal studies, 113 cattle, two mules, 28 chickens, 12 dogs and six cats located on farms within a two-mile radius of the farm on which the epidemic occurred were skin tested with histoplasmin. Of these, six cattle, one mule and two chickens reacted to the test, a total of nine reactors out of 161 animals tested, or 6%. It is not believed that this represents an excessive incidence of reactors among animals for this general area. These observations are reported in detail elsewhere.[4]

Isolation of H. capsulatum *from the Air:* Air sampling by use of a Venturi sampler on April 14, 1953, inside and outside the chicken house, resulted in isolation of *H. capsulatum* from the air two feet above the ground inside the house and six inches above the ground on the north side of the chicken house. The material collected was injected into mice.[3]

Discussion

Here, for the first time, the complete story of an epidemic of histoplasmosis is unfolded. We have the definite history of exposure to a point source from which the organism was isolated, not only by culture but also by sampling of the air. Here, too, the gamut of clinical manifestations of this disease is evident in this family. The mother had the fewest symptoms, developing only slight fever and headache, and never feeling ill enough to go to bed. The father had a somewhat more severe illness, which again was considered to be only influenza. The two younger sons had severe illnesses, lasting perhaps a week, which at the time were thought to be influenza. The father's younger brother had the most severe illness, lasting more than two months and requiring hospitalization for 70 days. We see, therefore, the clinical manifestations of histoplasmosis running from extremely mild to very severe. Also, the x-ray pictures demonstrate similar differences: the mother and father had only slight lesions, the two younger children had more severe lesions, and the brother-in-law, who had had the most exposure to the shoveling of infected material, had the most severe of all.

The infection of the animals on this farm illustrated the spread of this disease to other species. Reactors were demonstrated among dogs, chickens and cows, and positive isolations were obtained from dogs and a cat.

The serologic tests for histoplasmosis on all of the patients showed a positive reaction, even though studies were not obtained on most of the family until 75 days after onset of the illness. Serologic results in the patient most severely ill were strongly positive, and continued to be so for at least 557 days after onset. The serologic reactions on the remainder of the family in general tended to drop towards normal.

While the source and causation of this epidemic appear quite clear, interesting questions are raised as to the importance of chicken houses in the spread of the disease. Both Zeidberg and Ajello [5] and Larsh [6] have commented on the frequency with which positive isolations of *H. capsulatum* are obtained from chicken coops. It is also interesting to note that unused chicken coops appear to be more frequently positive than used ones. It is not clear whether this is because the organism is able to grow in the used chicken coops but multiplication is somewhat controlled by repeated cleanings, or whether the unused condition and drying of material within the chicken house create better possibilities for airborne dissemination with cleaning. It seems probable that the chicken houses provide the environment in which the organism grows, rather than that the chickens themselves serve as reservoirs. This is illustrated by the fact that only one chicken out of 27 reacted to a histoplasmin skin test, and cultures of this chicken were negative for the organism. The other interesting point brought out by this epidemic is that the amount of exposure is roughly proportional to the degree of illness. It is also interesting to note that, although the two younger children were fairly severely ill, they recovered without incident, although this disease is quite frequently fatal in young children. On the other hand, the boy of 16 who had the most severe illness also had the most extensive exposure to the cleaning of the chicken house.

The animal studies in this particular epidemic show quite clearly the relationship of infected premises to infected animals. Histoplasmin skin tests on animals in the neighborhood of the epidemic did not indicate an unusual prevalence of sensitivity in that area.

Summary

An epidemic of histoplasmosis involving both man and animals is reported. The source of the epidemic was established and the means of spread proved by the isolation of airborne organism from the source. The varieties of the clinical manifestations of histoplasmosis are well shown in the five persons involved in this epidemic. They varied from very mild to very severe.

Summario in Interlingua

Es describite un epidemia de histoplasmosis involvente un familia rural de 5 personas. Clinicamente le morbo in iste 5 personas variava inter un leve malaise influenzoide in le matre e le patre e un sever e prosternente disordine con un duration de 70 dies in le caso del fratre junior del patre. Le severitate del morbo esseva proportional al grado del exposition al materia infective, le qual esseva incontrate in remover desiccate excrementos ab un stabulo de gallinas. Omne le individuos involvite monstrava positive reactiones serologic e anormalitates in roentgenogrammas del thorace. *Histoplasma capsulatum* esseva isolate al puncto focal ab le desiccate excrementos e ab specimens de aere prendite in e circa le stabulo. Le examine del animales al ferma occupate per le patientes resultava in positive reactiones dermatic inter le bestial, le gallinas, e le canes. Culturas pro le fungo *H. capsulatum* esseva positive in 5 canes

e l catto. Tests dermatic in altere animales del vicinitate del ferma non revelava un inusual numero de reactores positive.

Le epidemia hic reportate illustra clarmente un varietate de manifestationes clinic—inter illos le marcate signos roentgenographic de pneumonitis disseminate in le caso le plus sever—e tractos specific tal como le association inequivoc con un puncto focal, le aerodiffusion del infection, e le frequentia de infection inter le diverse species animal al ferma.

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CASE REPORTS

IS PRIMARY HEMORRHAGIC THROMBOCYTHEMIA A CLINICAL MYTH?*

By WILLIAM R. MCCABE, M.D., *San Antonio, Texas,* ROBERT M. BIRD, M.D., and ROBERT A. MCLAUGHLIN, M.D., *Oklahoma City, Oklahoma*

TRANSITORY thrombocytosis is seen following splenectomy, during the postpartum period and accompanying certain infections and malignant processes.[1] More persistent elevations of circulating blood platelets, that is, thrombocythemia, are occasionally seen in polycythemia rubra vera[2] and chronic myelogenous leukemia.[3] In addition, 13 cases have been reported in the literature in which a persistent thrombocythemia was attributed to a primary dyscrasia of the megakaryocytes and platelets. This syndrome has been referred to as primary hemorrhagic thrombocythemia. We wish to present another case in which the diagnosis of primary hemorrhagic thrombocythemia was made. It was possible to follow this patient throughout the entire course of his disease and to establish quite clearly that his primary disease was leukemia. In addition, the previous 13 cases will be reviewed. It is our opinion that there is insufficient evidence to warrant the classification of any of these 14 cases in a separate disease syndrome, but rather that the elevation of platelets which all cases manifested was but another variant of a more usual hematologic disorder.

CASE REPORT

A 44 year old white male abstractor was in good health until September, 1950, at which time he noted the onset of intermittent but progressive numbness, tingling and cyanosis of the fingers of the right hand. In succeeding months he developed transitory attacks of dizziness, tinnitus, scotomata, occasional nausea and vomiting, and intermittent bouts of epigastric pain relieved by milk and soda. In February, 1951, he consulted his physician because of these symptoms, a loss of 15 pounds in weight, and the passage of a single black stool. Physical examination at that time was unrevealing, and he was referred to another clinic.

Studies at this clinic in February and March, 1951, revealed a normocytic anemia, slight leukocytosis, marked and persistent basophilia, and a persistent thrombocythemia with a peak value of 6.2 millions per cubic millimeter. These and subsequent laboratory studies are summarized in tables 1 and 2. A sternal marrow aspiration and biopsy both demonstrated myeloid hyperplasia with increased numbers of megakaryocytes. X-ray studies of the chest and gastrointestinal tract showed no pathologic change. On the basis of these findings the diagnosis of primary hemorrhagic thrombocythemia was entertained. In June, 1951, the patient received two whole blood transfusions and a course of total body irradiation of unknown dosage. Be-

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From the Departments of Medicine and Pathology, University of Oklahoma School of Medicine, and University Hospitals, Oklahoma City, Oklahoma.

TABLE 1
Peripheral Blood

Date	HGB gm.	RBC 10^6	Platelets 10^4	WBC 10^3	PMN	Metamyelo.	Myelo.	Promyelo.	Myeloblast	Lymph.	Mono.	Baso.	Eos.	Remarks	Miscellaneous
2–13–51	12	3.5		13	81					15	3		1	Toxic granulation	Hematocrit = 43%
2–20–51	11.5	3.7	6.3	12	57					20	2	15	6		B.T. = 1'30", C.T. = 6"
6–18–51	10	3.1	4.6	17	58	2	1	1		16		15	7		Hemat. = 29%
															Retics. = 3%
8–9–51	11.6	3.6	1.9	13	56				1	19		18	7	Nucl. RBC's	Uric acid = 3.5
															Prothrombin = 16"
10–8–51	11.5	4.0	1.3	5	65					13		17	5	Toxic granulation	N.P.N. = 29
2–7–52	10.5	3.8	0.4	13	77					8	2	11	2		
6–12–52	12.7	4.1	1.7	25	56				2	15	1	22	4	Nucl. RBC's	van den Bergh = 0.75
															Uric acid = 3.2
12–9–52	11.8	4.0	0.9	19	63	4	3	2	1	9	2	13	3		Cholesterol = 162
															Alk. P'ase = 2.4 BU
2–18–53	11.8	4.1	0.5	39	39	23	6	4	2	5		20	1		Phosphorus = 4.4
															Prot. Bd. I_2 = 5.5 gamma
3–22–53	13.5		0.1	62	15	1	23	22	25			10	4		Coombs' = Neg.
4–3–53		3.1	0.4	314	3	2	17	24	36	11	1	5	1	Nucl. RBC's	Total Prot. = 3.3/1.8
															NPN = 33

TABLE 2
Sternal Marrow

Date	Adult PMN	Meta-myelo.	Myelo.	Pro-myelo.	Myelo-blast	Baso.	Eosino.	Mono.	Lymph.	Young Lymph.	Normo-blast	Un-classified	? "Blast"	Remarks
2–23–51	27	9	← 20	→	6	←	— Unknown —	→			11			Normally cellular marrow. Trephine biopsy.
3–30–51														
8–10–51	23	23	12	4	3	5	5	0	6	0	16	1	2	Masses of megakaryocytes.
12–9–52	36	13	12	6	1	3	3	0	6	0	11	3	6	Masses of megakaryocytes and platelets Marked increase in megakaryocytes
2–18–53	8	8	6	25	37	1	4	0	8	0	3	1	0	

cause of the persistence of symptoms and continued loss of weight, he was referred to University of Oklahoma Hospitals in July, 1951.

Pertinent past history revealed eight x-ray treatments of 75 r weekly in 1924 for generalized acne. He also received an additional unknown amount of irradiation for a fungus infection of the hands in 1944. The family history revealed that the patient's father had died of gastric carcinoma.

Physical examination showed evidences of recent loss of weight, as well as old acne scars covering the patient's face, trunk and back. The tip of the spleen was palpable, but there was no lymphadenopathy, purpura or gingival bleeding. The previous laboratory studies were confirmed, and it was the consensus that the patient had primary hemorrhagic thrombocythemia, although chronic myelogenous leukemia could not be excluded. He was given 8.31 millicuries of radioactive phosphorus. Vertigo decreased, general strength improved and bowel bleeding ceased.

In February, 1952, he had a two-week bout of recurring hemoptysis. No source of bleeding was noted in the nasopharynx. X-ray examination of the chest was remarkable only for increased bronchovascular markings. In June, 1952, a low grade afternoon elevation of temperature was noted, and in the following month the patient had recurrent attacks of sharp, localized pain in the left lower quadrant unassociated with nausea, melena, colic or constipation.

When he was seen in August, 1952, physical examination revealed the development of lymph nodes 1 cm. in diameter in the anterior cervical chain and in the left axillary region. Sternal tenderness was elicited. A nontender liver edge was palpable 1 cm. below the right costal margin. The spleen was readily felt. Study of the peripheral blood showed a marked leukocytosis, characterized by immaturity of the neutrophilic series associated with pronounced basophilia. The anemia had improved. The number of circulating platelets continued to be elevated

The patient did not return to our institution for further studies until December, 1952. At that time sternal marrow aspiration showed a tremendous increase in the number of megakaryocytes. There was a shift to the left in the granulocytic series. Bone survey and x-rays of the upper gastrointestinal tract showed nothing remarkable. There was no evidence of increased hemolysis of erythrocytes.

In January, 1953, following a respiratory infection, all previous symptoms became markedly aggravated. Generalized bone pain developed. The lymph nodes in all areas rapidly enlarged, and the patient noted the appearance of nodules in the skin of the trunk, extremities and scalp. He was again hospitalized in February, 1953. Biopsies of both the lymph nodes and the skin showed areas of leukemic infiltration. The peripheral leukocyte count was now in the range of 50,000, with an extreme shift to the left of the granulocytic series. The circulating platelets were normal in number. Sternal marrow aspiration revealed a picture typical of myeloblastic relapse of chronic myelogenous leukemia. In the succeeding two months the patient received two courses of radioactive phosphorus totaling 6 and 10.5 millicuries, respectively. His clinical course rapidly deteriorated with the progression of all physical signs. He died quietly April 5, 1953. Postmortem examination was performed six hours after death.

Necropsy Findings: The body was poorly nourished. Superficial lymph nodes were not enlarged, and numerous ecchymoses covered approximately 20% of the body surface. The skin appeared thickened by many small yellow papules which in some areas were confluent. Cut surfaces of skin suggested infiltration of the dermis by light yellow tissue. The liver weighed 2,700 gm. Its capsular surfaces were slightly mottled with yellowish flecks similar to the skin papules. There was yellowish discoloration of the periportal areas which gave the cut surfaces a uniform and finely mottled appearance. The spleen weighed 1,440 gm. The capsule was smooth and a dark reddish purple. Cut surfaces presented a rather homogeneous appearance,

and the malpighian corpuscles were indistinct. The pulp was firm. The periaortic, peripancreatic and other abdominal lymph nodes were all enlarged several times normal size, firm, matted together, and light yellow. The gastrointestinal tract was not remarkable. The kidneys weighed 200 and 195 gm., respectively, and showed a finely nodular infiltration of the cortex similar to that seen in the skin and liver. The left pleural cavity contained approximately 1 L. of slightly cloudy yellow fluid, but the right was dry. The left lung weighed 440 gm., the right, 600 gm. Congestion, compression atelectasis and yellowish infiltration about all air passages were apparent. Paratracheal and peribronchial lymph nodes were enlarged. The pericardial cavity was not remarkable. The heart muscle was rather flabby and paler than normal. Multiple sections through bone revealed a very abundant grayish yellow marrow.

On microscopic examination there was extensive leukemic infiltration of most organs, especially bone marrow, lymph nodes, spleen, liver, kidneys and skin, where the normal architecture was virtually obliterated. In addition, there were many foci of perivascular infiltration in the lungs, epicardium and brain. The leukemic cells were poorly differentiated and exhibited anaplasia and moderate pleomorphism. Peroxidase stains were negative. The hepatic infiltrates showed a striking tendency to periportal localization.

Discussion

In 1934 Epstein and Goedel [4] postulated a primary blood dyscrasia of the megakaryocytes and platelets which they named primary hemorrhagic thrombocythemia. A previous report of this case [5] had considered the possibility of polycythemia rubra vera showing an abnormal number of circulating blood platelets. Uotila [6] reported a similar case and re-analyzed another reported by Di Guglielmo.[7] Both were considered to be primary platelet disorders. Di Guglielmo had considered his case as one of erythroleukemia with an abnormally elevated peripheral platelet count. Several additional cases were reported in the literature, one by Reid in 1940.[8] This author characterized primary hemorrhagic thrombocythemia as a dyscrasia of the megakaryocytes and platelets showing an increased number of circulating blood platelets, a tendency to thrombosis and hemorrhage, a moderate leukocytosis, an increase in the number of megakaryocytes in the bone marrow, polychromasia, anisocytosis, and poikilocytosis with or without anemia. To the criteria given by Reid we should like to add still another, namely, that the patient be followed for a period of time sufficient to be certain that the symptoms and signs enumerated above are not manifestations of a more clearly defined hematologic disorder. Our patient was initially considered to fulfill the criteria of Reid. His course stimulated us to re-analyze those cases previously labeled primary hemorrhagic thrombocythemia.

Table 3 gives selected data from the 13 cases previously reported in the literature. Added to these is the present case. The cases have been grouped according to their similarities. The first six cases all showed, at one time, a pathologic elevation of erythrocytes, in addition to thrombocythemia. Case 1 was considered by its author to be erythroleukemia, and was characterized by an increased number of all the formed elements produced by the marrow. The length of follow-up is unknown, and no pathologic studies are available. Case 2 came to necropsy after a clinical course suggesting polycythemia rubra vera.

TABLE 3

Case	Author	Author's DX	Platelets 10^6	RBC 10^6	WBC 10^3	Peripheral Smear	Marrow	Necropsy	Length of Follow-Up	Our Suggested Diagnosis
1	DiGuglielmo	"Piastrinemia"	Marked increase	7.5	20	Granulocytosis, increased megakaryocytes	No report	Surviving	?	Polycythemia
2	Epstein, Kretz, Goedel	P.H.T.	1.2 to 2.2	7.5	20	Granulocytosis, monocytosis, eosinophilia		Splenic atrophy		Polycythemia
3	Uotila	P.H.T.	0.5 to 5.0	7.3	44	Granulocytosis with eosinophilia	Megakaryocytes, normoblasts increased	None	18 mos.	Polycythemia
4	Rowlands, Vaizey	P.H.T.	0.5 to 1.8	7.2	18	Granulocytosis	No report	Surviving	14 mos.	Polycythemia
5	Lebel	P.H.T.	0.4 to 1.2	5.3 to 7.0	44	Granulocytosis with myelocytes	5% Megaloblasts	Surviving	?	Polycythemia
6	Mortenson	P.H.T.	1.5 to 6.0	9.8	53	Granulocytosis	10% Promyelocytes 18% Myelocytes 10% Nuc. RBC's	Surviving	6 yrs.	Polycythemia and/or leukemia
7	Drake	Myel. Leuk.	1.0 to 2.6	5.8	33	Granulocytosis, leukoblasts and megakaryocytes	No report	Surviving	5 mos.	Leukemia

TABLE 3—*Continued*

Case	Author	Author's DX	Platelets 10^6	RBC 10^6	WBC 10^3	Peripheral Smear	Marrow	Necropsy	Length of Follow-Up	Our Suggested Diagnosis
8	Akazaki, Hamaguchi	P.H.T.	0.02 to 28	3.4	0.3 to 15	Granulocytosis	10% "Megakaryoblasts"	TBC; marrow, liver, spleen infiltrated	10 mos.	Leukemia
9	Rowlands, Vaizey	P.H.T.	0.3 to 1.9	2.8 to 4.7	5 to 17	Eosinophilia	No report	Surviving	5 yrs.	Idiopathic steatorrhea
10	Reid	P.H.T.	1.7 to 3.8	4.6 to 5.1	14 to 18	Granulocytosis	Myeloblasts—3% Promyelocytes—29%	Surviving	5 mos.	Inadequate follow-up
11	Owren	P.H.T.	0.2 to 1.4	4.4 to 4.8	8 to 13	"Normal"	Increased plats. Megakaryocytes	Surviving	?	Inadequate follow-up
12	Holst	P.H.T.	0.6 to 0.9	4.9 to 5.9	19 to 31	"Normal"	Hyperplastic	Surviving	5 yrs.	Inadequate data
13	Spangberg, Zettergren	P.H.T.	0.2 to 5.2	2.7 to 3.9	8 to 70	Granulocytosis	Megakaryocytes numerous	Post-splenectomy, gastric carcinoma	6 mos.	Post-splenectomy, thrombocytosis
14	McCabe, Bird, McLaughlin	Myel. Leuk.	0.04 to 6.3	3.0 to 5.2	5 to 314	Granulocytosis	Numerous myeloblasts, megakaryocytes	Leukemia	26 mos.	Leukemia

The authors contended that such was not the diagnosis because of the finding of an atrophic spleen. We believe that such a pathologic finding may have represented the result of multiple splenic infarcts and need not be sufficient cause to question the diagnosis of polycythemia. Cases 3 through 6 [6, 9, 10, 11] likewise all showed pronounced erythrocytosis. Each showed a marked leukocytosis as well as thrombocythemia. No necropsy studies were performed on case 3, and cases 4, 5 and 6 were surviving at the time of the report. We feel that each of these six cases can more reasonably be diagnosed as a variant of polycythemia rubra vera. The finding of extreme degrees of thrombocythemia in primary polycythemia has been well documented by Dameshek and Henstell.[2] Twelve of 20 cases reported by these authors had platelet counts in excess of 1,000,000 per cubic millimeter.

Case 7, that of Drake [12] was considered by the author to represent myelogenous leukemia. We concur from the data which he presented and are not deterred from this diagnosis by the presence of a persistent thrombocythemia. Case 8 [13] represented a complex clinical picture complicated by tuberculosis, syphilis and typhoid fever. Whether the reported "blast" cells found in the peripheral blood and the bone marrow represented a leukemoid reaction or a true leukemia is not clear, but the postmortem examination would seem to support the view that the patient also had leukemia. In this case, the authors classified the immature cells found at post mortem as megakaryoblasts. Such a morphologic differentiation is certainly open to question. As early as 1925 Minot and Buckman [3] pointed out that thrombocythemia occurred in chronic myelogenous leukemia in as high as 20% of cases. The terminal fall of the platelets in case 8 gives further support to the notion that leukemia was the primary blood disorder.

Cases 9 through 12 seemed to represent a variety of disorders, having in common only increased circulating platelets. None of these cases came to necropsy. Case 9 [9] seemed clinically to answer the description of idiopathic steatorrhea. Case 13 [14] developed a marked thrombocythemia only following splenectomy and at post mortem was found to have a gastric carcinoma. Cases 10,[8] 11 [15] and 12 [16] have insufficient data to enable one to make a definitive diagnosis.

There is an increasing volume of evidence to indicate that leukemia [17] and perhaps other well recognized hematologic entities may exist for considerable periods of time showing bizarre laboratory findings. Only after protracted follow-up does the true nature of the disorder become clear. The case reported here is representative. Under such circumstances, and despite opinions to the contrary,[16] it would seem more profitable to refrain from postulating new syndromes until all the evidence available in an individual case has come under careful scrutiny.

Summary

1. A patient with chronic myelogenous leukemia is reported in whom the initial diagnosis was primary hemorrhagic thrombocythemia.

2. The previous literature pertaining to this syndrome has been reviewed. It is the authors' opinion that in no case in which sufficient data were available

was it necessary to postulate a primary dyscrasia of megakaryocytes or platelets to account for the thrombocytosis.

ACKNOWLEDGMENT

Acknowledgment is made to Dr. Simon Dolin for his assistance with the bibliography, and to the staff of the Scott and White Clinic for the data supplied on the case here reported.

SUMMARIO IN INTERLINGUA

Le caso de un masculo blanc de 44 annos de etate esseva sequite durante un maladia de duo e medie annos. Nos presenta le constatationes clinic e necroptic. Al initio le patiente presentava symptomas e signos suggerente le presentia de multiple parve thromboses vascular. Il occurreva un persistente e pronunciate augmento del plachettas e megacaryocytos. Le diagnose de primari thrombocythemia hemorrhagic esseva formulate. Durante le 6 menses terminal del vita de iste patiente, le constatationes clinic esseva integremente compatibile con leucemia myeloblastic. Studios microscopic executate post le necropsia supportava le diagnose de leucemia.

Nos presenta un revista del disponibile litteratura super primari thrombocythemia hemorrhagic. Nos es frappate per le observation que in omne casos reportate in le litteratura, providite que adequate observationes a longe durantia es includite, il es possibile explicar le configuration clinic como un variation inusual de un altere disordine hematologic de character plus commun e ben establite.

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MULTIPLE MYELOMA: REPORT OF A CASE SHOWING UNUSUAL REMISSION LASTING TWO YEARS FOLLOWING SEVERE HEPATITIS *

By ROSE E. LONDON, *M.D., Miami Beach, Florida*

IN the past 25 years multiple myeloma has been regarded with interest because of the increasing number of reported cases,[1, 2, 3, 4] the curious associated abnormalities in protein metabolism, and the clinical trial of certain new drugs. In the growing literature accounts of spontaneous remission are rare, and effective therapy is lacking. Sporadic cases in which radioactive phosphorus,[5] urethane,[6] stilbamidine[7] or adrenocorticotropic hormone[8] have produced remissions for variable periods of time are exceptional.

The following case of multiple myeloma is reported because of the spectacular and complete remission in the clinical and hematologic aspects of the disease for a period of two years before a recurrence led to death. The cause of the remission is unknown, but its relationship to the appearance of a hepatitis is discussed.

CASE REPORT

A 39 year old white housewife was first seen on February 20, 1950, at which time she complained of increasing weakness and a 10 pound weight loss over the preceding eight months. One year before she had noted the gradual appearance of yellow pigmentation of the skin of the eyelids and axillae. Eight months before, following the onset of weakness, she had been examined by another physician and found to have an anemia which did not respond to liver injections and iron tablets. Over the ensuing eight months the weakness became more marked and was associated with a 10 pound weight loss, anorexia and a severe paroxysmal cough productive of mucoid sputum. Nosebleeds occurred daily for one month, but no other hemorrhagic tendency was noted. Her past history was uneventful except for epigastric pain five years before, at which time gall-bladder and stomach x-rays were found to be normal. There had been one normal pregnancy 14 years before, preceded by a single spontaneous abortion.

Physical examination revealed a chronically ill, 39 year old white woman. There was a diffuse yellowish discoloration of the skin in both axillary areas, and wide orange-yellow pigmented bands encircling the nasal half of the eyelids. The unaffected skin and the mucous membranes were pale, and there was oozing of blood from a small erosion of the nasal septum. The remainder of the examination was normal except for a mass in the abdomen, deep in the right upper quadrant, which moved with respiration and appeared to be in the right kidney.

The following laboratory work was done over the ensuing month while she was an ambulatory patient and during the first hospitalization at Mount Sinai Hospital, March 15 through March 19, 1950. Blood studies showed red blood cells to be 3.08 million per cubic millimeter; hemoglobin, 8.5 gm.; white blood cells, 17,900, with a differential count of polymorphonuclear leukocytes, 47%; lymphocytes, 51%; myelocytes, 1%; monocytes, 1%. The smear showed marked rouleau formation. Platelets were 60,000 per cubic millimeter. The hematocrit was 20 mm. Bleeding time was normal; clotting time was prolonged (45 min. capillary method, 20 min. Lee White).

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From the Departments of Medicine and Pathology, Mount Sinai Hospital of Greater Miami, Miami Beach, Florida.

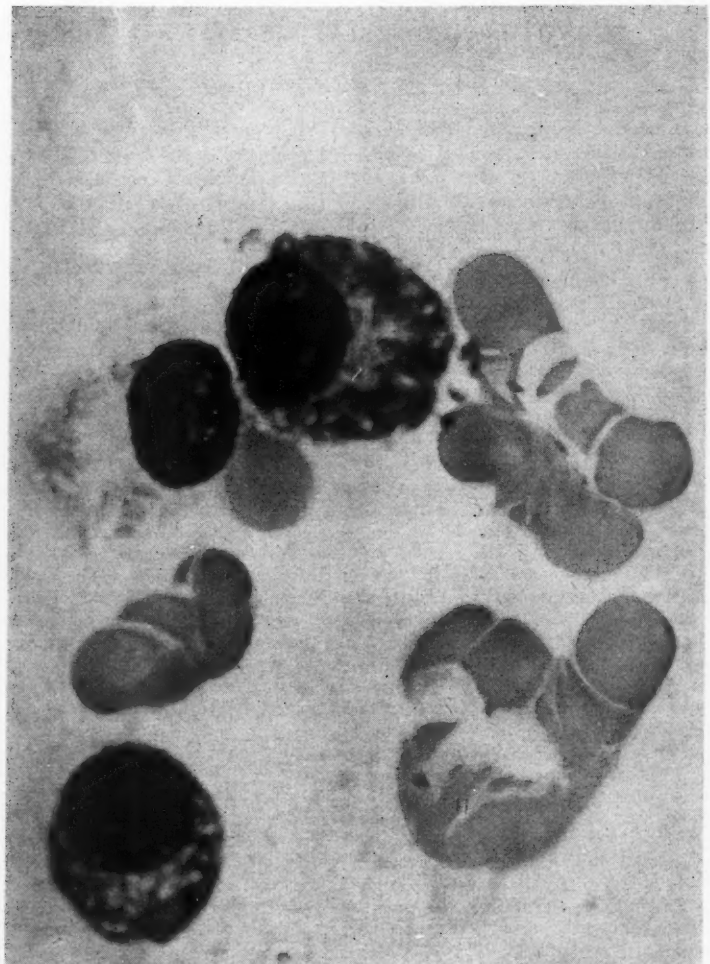

FIG. 1. Bone marrow smear during activity of the disease, showing the myeloma cells, which constituted 90% of the marrow cells. (× 2022 magnification)

Clotted blood formed a solid gel with little retraction in 24 hours. Urinalysis was normal, and no Bence Jones protein was detected. Sternal marrow smear showed plasma cells, 74%; lymphocytes, 2%; polymorphonuclears, 6%; bands, 10%; metamyelocytes, 6%; myelocytes, 2%. The plasma cells showed great variability in form, ranging from immature to adult type (figure 1). The blood chemical values per 100 c.c. blood were calcium, 8.2 mg.; phosphorus, 4.3 mg.; bilirubin, 0.12 mg.; total cholesterol, 228 mg., and protein, 12 gm., with 9.35 gm. globulin and 2.65 gm. albumin. Frei test was negative. Gastric analysis showed 51 u. of free hydrochloric acid after histamine. Stools were negative for blood and parasites. X-rays of the long bones, chest, skull and kidneys were normal, except for slight demineralization of the pubic bones.

Upon the establishment of the diagnosis of multiple myeloma the patient was sent to a hospital in another area to receive adrenocorticotropic hormone. Here the diagnosis was confirmed. Studies for cryoglobulin and cold agglutinins in the blood were negative. A 2 plus albuminuria was noted for the first time, and the blood urea nitrogen was 21 mg. %. The patient received ACTH for 25 days, in doses varying from 50 to 100 mg. daily, in addition to 4,500 c.c. whole blood, without benefit. Upon returning to our care in June, 1950, urethane therapy was started in 3 gm. daily doses for four months. During this time she lost an additional six pounds, and complained of severe anorexia, repeated vomiting, nocturnal diarrhea, pain and numbness in the right leg, and pain and weakness of both hands. An attack of acute herpes zoster of T 12 on the left side occurred but cleared in several weeks. Repeated transfusions were necessary, and it was obvious that the patient was deteriorating despite therapy.

On September 8, 1950, because of the onset of itching and yellow discoloration of the skin, more frequent vomiting, and right upper quadrant pain, urethane was discontinued and the patient was hospitalized for the second time at Mount Sinai Hospital. She was acutely ill, with marked jaundice and an enlarged, tender liver. The icteric index was 60 u.; total cholesterol, 250 mg. per 100 c.c., with cholesterol esters of 93 mg. %; cephalin flocculation was 4 plus, and the prothrombin time was 21 seconds (control, 14 seconds). Temperature fluctuations between 100° and 103° F. occurred daily, jaundice increased, and the patient became alternately drowsy or hyperirritable. Aureomycin was given in 250 mg. doses every four hours for two weeks. On the seventh day ascites first appeared, the icteric index increased to 84, and a painful eruption of herpes zoster rapidly involved the left side of the neck and ear. The patient became increasingly dyspneic, cyanotic and stuporous. The ascitic fluid accumulated rapidly, together with edema of the legs, necessitating abdominal paracentesis with removal of 6,500 c.c. yellow fluid. After five days in this moribund condition the patient began to improve. Over the ensuing four weeks the icteric index dropped, fever disappeared and the patient became alert. The liver decreased in size and tenderness. At this time it was noted that the red blood cells numbered 4.7 million per cubic millimeter, with 15 gm. hemoglobin; the total protein was 8.88 gm., with albumin, 1.59, and globulin, 7.29 gm.

The patient was discharged on October 15, 1950, and required several more paracenteses and frequent mercurial diuretics for ascites. By the end of November, 1950, marked improvement was apparent, peripheral edema and ascites completely disappearing, and the red blood count remaining around 4.5 million per cubic millimeter, with 17 gm. hemoglobin. Albuminuria disappeared and the total protein dropped to 6.4 gm.

For the following two years the patient showed a spectacular and complete remission of all symptoms, gained 25 pounds of weight, and was the picture of radiant health. She was able to return to work and felt completely well. Her monthly blood count, urine and total protein of the blood remained within normal limits, the red cell count never falling below 4.2 million per cubic millimeter, with 14 gm.

hemoglobin. A sternal marrow aspiration differential on July 3, 1952, was normal, with 3% plasma cells of adult type.

On December 11, 1952, slightly more than two years following the disappearance of signs and symptoms of multiple myeloma, the patient presented herself in the final recurrence of her disease, with the complaint of pain, numbness, and burning and weakness of both hands. There were slight pallor of the skin and mucous membranes, the pigmentation of the eyes and axillae as previously described, and an erythematous appearance of the palmar surface of the hands. There was diminution in sensation (touch, pain, two-point discrimination and proprioception) in both hands from the metacarpophalangeal joints to the fingertips. The blood count revealed 2.96 million red cells per cubic millimeter, with 11.9 gm. hemoglobin and 9,500 white blood cells. The differential showed 32% polymorphonuclears, 34% band cells, 25% lymphocytes, 1% monocytes, 4% basophils, 2% myelocytes, 2% promyelocytes. The total protein was 15.6 gm. per 100 c.c., with 2.5 gm. albumin and 13.1 gm. globulin.

The patient was hospitalized for the third time at Mount Sinai Hospital, from December 22 to December 29, 1952, where search was made for a possible infectious etiology. Blood and sternal marrow cultures, agglutinations for typhoid, paratyphoid, brucella, Weil-Felix, and blood smears for malaria were all negative. Skin tests with trichina antigen, coccidioidin, blastomycin and histoplasmin were negative. Sternal marrow aspiration revealed sheets of myeloma cells, varying in morphology from immature to mature, and comprising about 90% of the marrow cells. Total protein was 12.6 gm. %; 2.1 gm. albumin and 10.5 gm. globulin. Electrophoretic studies showed alpha globulin 0.5 gm.; beta globulin, 0.7 gm.; gamma globulin, 9.3 gm.; thymol turbidity was 31.6 u. Prothrombin time was 17 seconds (control, 14 seconds); alkaline phosphatase, 2.2 u., and cholesterol, 240 mg. %, with 169 mg. % cholesterol esters. Blood calcium was 12.8 mg. %, the Bromsulphalein test was normal. A lupus erythematosus preparation was negative. X-rays of the long bones and skull were negative.

Over the subsequent two months the patient failed rapidly. The pain and disability of the hands were excruciating, requiring repeated narcotics for relief. A severe paroxysmal cough reappeared which failed to respond to antibiotics. Because of intractable vomiting following oral urethane, it was finally decided to attempt intravenous therapy. She was admitted for the fourth time to Mount Sinai Hospital on March 17, 1953. A total of 25 gm. of urethane was given intravenously over a 10 day period. Daily white counts were taken and the patient tolerated the medication well. Two days after discharge from the hospital she developed severe pain and tenderness of the right shoulder, and the upper arm was swollen and slightly mottled. Over the following 24 hours she became feverish and disoriented, and was hospitalized for the fifth time at Mount Sinai Hospital on March 31, 1953. She was acutely ill, dehydrated and disoriented. The temperature was 104° F.; pulse, 120; respiration, 42. The right upper arm was swollen with ecchymosis of the overlying skin. X-ray of the chest was normal. Blood count showed 2.94 million red cells per cubic millimeter, with 8.43 gm. hemoglobin and 8,750 white blood cells. The differential showed 19% polymorphonuclear leukocytes, 22% band cells, 12% lymphocytes, 12% monocytes, 9% metamyelocytes, 11% myelocytes, 15% plasma cells. There were 4 nucleated red cells per 100 red cells, and marked anisocytosis with microcytes and macrocytes and polychromatophilia.

The patient's condition rapidly deteriorated and she died four hours after admission.

Postmortem Examination: The basic pathologic lesions in this patient lay in the ribs, sternum, vertebrae, lungs, liver, spleen and kidney.

The ribs, sternum and vertebrae grossly showed an infiltration of white tissue producing an irregular mottled appearance of the marrow. Histologically, sheets

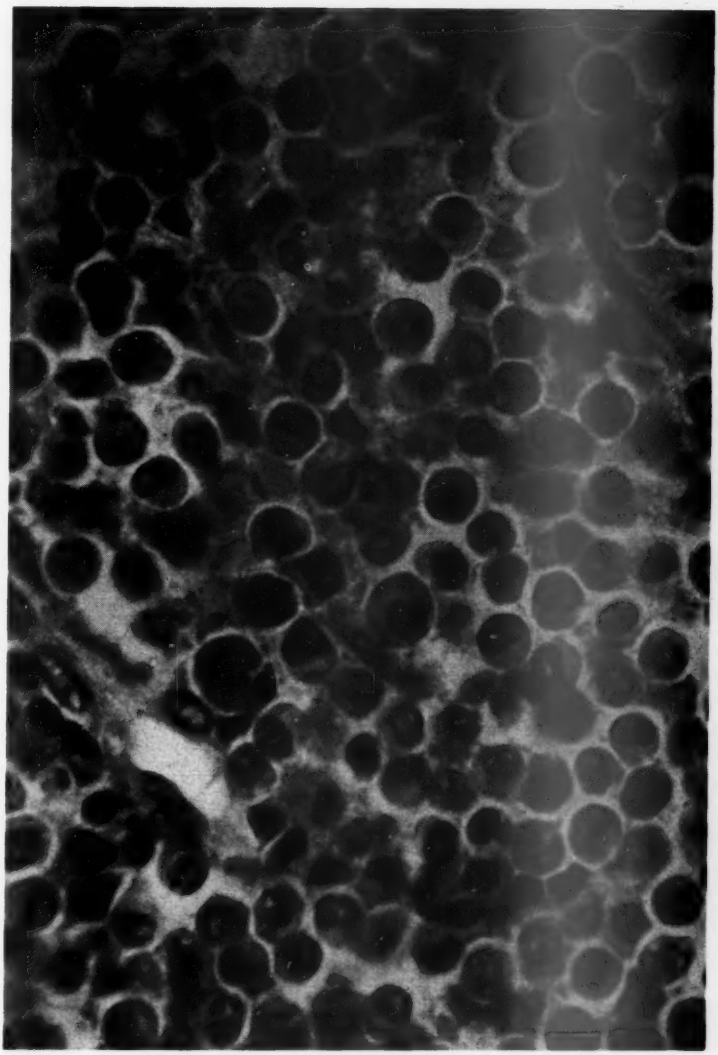

FIG. 2. Postmortem section of the bone marrow, showing marked infiltration with plasma cells. (× 1,100 magnification)

of mononuclear cells replaced the normal bone marrow cellular pattern. Some of these cells resembled plasma cells, while others were larger, with larger, paler nuclei with more delicate chromatin and less basophilic cytoplasm. These cells were considered young plasma cells. These cells did not differ in size and shape, and only occasional mitotic figures were in evidence. Similar cells of the more matured type were found in the lungs, liver, spleen and kidneys (figure 2).

The liver weighed 1,850 gm. It was irregularly, finely nodular, and puckered on section. Histologically there was a moderate to marked increase in connective tissue, with disruption of architecture. The bile ducts were proliferated. The periportal connective tissue was infiltrated with lymphoid cells, and few plasma cells.

The spleen weighed 480 gm. The red pulp was markedly infiltrated with cells similar to those present in the bone marrow.

The kidneys together weighed 290 gm. Histologically, in addition to the slight plasma cell infiltration, the glomeruli were swollen with filling of the tufts. The convoluted tubules were likewise markedly swollen and showed degenerative and necrotic changes. The epithelium of the collecting tubules was proliferated, and the tubules contained various types of casts.

The lungs were rubbery in consistency; and histologically, in addition to the focal plasma cell infiltration, there was a marked proliferation of fibrous tissue in the septa. The heart showed a relative hypertrophy of the right ventricle with an infiltration of fat.

The pathologic diagnosis was: (1) multiple myeloma with involvement of the ribs, sternum, vertebrae, lungs, liver, spleen and kidneys; (2) portal cirrhosis; (3) nephrosis; (4) pulmonary fibrosis, and (5) cor pulmonale.

Discussion

The picture of multiple myeloma as presented by this patient was of a rapidly progressive disease of approximately eight months' duration in which the clinical course, the pleomorphic appearance of plasma cells in the bone marrow, and the profound changes in the blood forbode an early termination. The poor prognosis was confirmed by the failure to respond to adequate therapy with adrenocorticotropic hormone and urethane. The onset of a serious liver involvement, with jaundice and ascites, rapidly led to a moribund state. Following a week of hepatic coma there was noted an unexpected reversal of the clinical condition, with complete recovery not only from the liver disease but also from the symptoms and signs of multiple myeloma. For two years the patient felt completely well, and monthly hematologic and total protein studies revealed no abnormalities. Even the bone marrow at the end of 21 months apparently was normal.

Two features of this remission should be emphasized: (1) its length, and (2) its completeness. In general, the prognosis of multiple myeloma from the onset of symptoms to death is between 18 and 24 months. Of the 64 cases reported by Snapper,[8] the average duration of life was 20 months. The patients surviving longer are apt to show single or multiple bone lesions[10, 11] rather than the generalized form of the disease. A survey of the literature fails to reveal any prolonged remissions due to therapy except for the following two cases. Snapper[8] reported a patient who survived 10 years and enjoyed a remission for about six years following stilbamidine. Bayrd[5] published a case in a moribund state who was treated with radioactive phosphorus and

made a complete recovery and was alive and well at least six and one-half years after the acute illness.[6]

The completeness of the recovery is the second spectacular feature. In the 51 cases reviewed by Meacham,[2] urethane gave relief of bone pain and variable subjective improvement but no alteration of the anemia or serum globulin. Rundles'[7] patients, also treated with urethane, showed some diminution of the serum globulin in five of 11 cases reported, while two others who responded symptomatically had no changes. In our case, the clinical status was completely normal, as were the peripheral blood, bone marrow, and the total protein of the blood.

It is interesting to conjecture as to the cause of this unusual remission. The possibilities are:

1. Spontaneous remission occurred.
2. Withdrawal of urethane resulted in improvement.
3. The liver disease had either a suppressive effect upon the myeloma process, or a stimulating effect upon the resistance of the patient.

While we cannot deny the first possibility, it is difficult to conceive of a sudden, spontaneous reversal in the face of the rapidly progressive course that our patient exhibited, with continuous weight loss, anemia, and marked derangement of bone marrow and protein metabolism.

In reference to the withdrawal of urethane, Rundles observed that, in several of his patients showing little response to urethane, marked improvement followed cessation of the drug. After studying the effect of urethane on yeast cells and sea-urchin eggs, he surmised that urethane may compete with natural amides in the biosynthesis of nucleotides. During prolonged therapy the myeloma cells may actually become dependent upon urethane for their metabolism, so that, following withdrawal, the growth of these cells may be suppressed. In our case the appearance of a severe hepatic disease after three months of urethane therapy led to the suspicion that we might be dealing with an acute necrosis of the liver due to urethane, such as has been described in experimental work in rats [12] and in clinical studies.[13, 14] The pathologic changes seen in urethane toxicity are disruption of the walls of the sinusoidal capillaries, with extravasation of serum and blood, and secondary necrosis of liver cells, most intense in the pericentral vein areas. In our case, however, we could not detect residual changes of this type. On the contrary, the liver had the appearance of a healed hepatitis, with proliferation of bile ducts, increase in periportal connective tissue and focal disruption of the architecture of the lobules. The frequency of previous transfusions offered an adequate explanation for a serum hepatitis (figures 3 and 4).

Finally, we considered that the marked derangement of metabolic processes produced by severe hepatocellular damage had a prolonged suppressive effect upon the myeloma cell. It has been noted that acute infections occasionally alter the course of chronic infections or malignancies. A recent review [15] on the subject attempts to explain some of the unusual and spectacular remissions of cancer following infections or administration of bacterial toxins. These alterations may occur directly through chemical or toxic effects, or through metabolic antagonism of cellular growth; or the environment of the cell may be un-

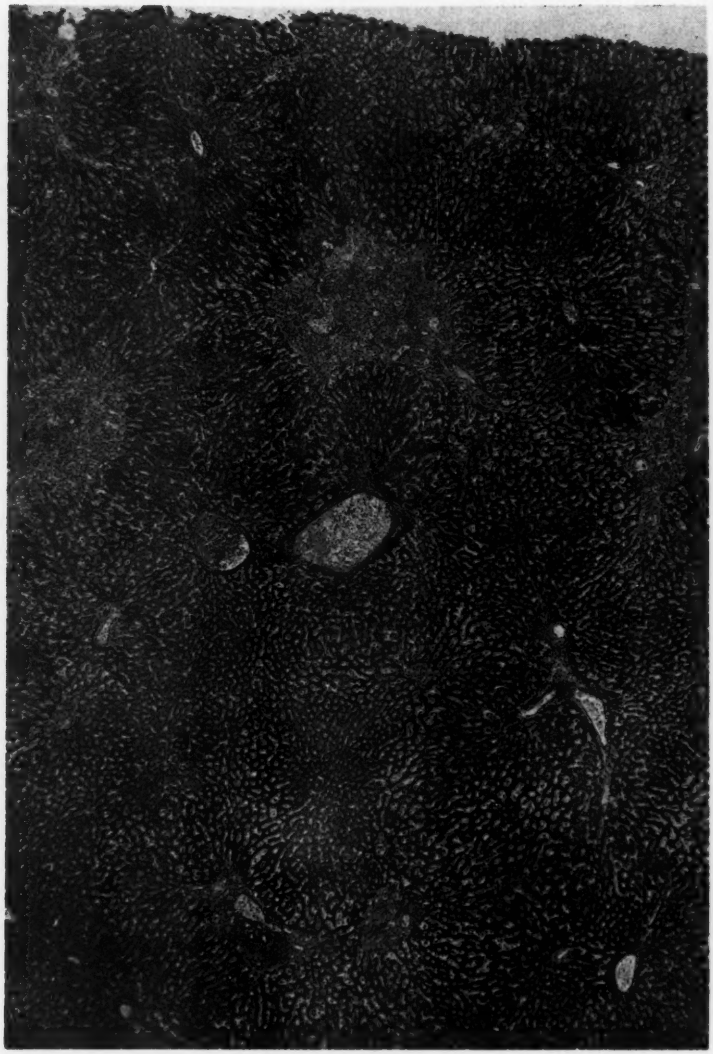

FIG. 3. Postmortem section of the liver, showing distortion of the architecture by periportal fibrosis and the absence of pathology in the central vein areas. (× 31 magnification)

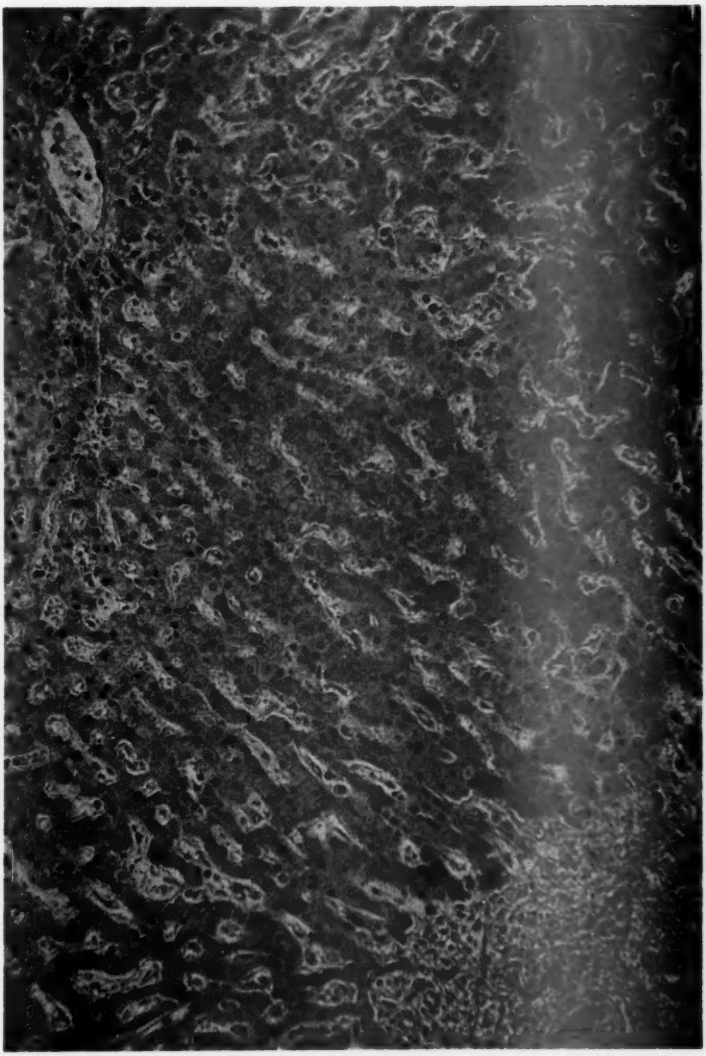

FIG. 4. Postmortem section of the liver under higher power, showing the pathology to be in the periportal areas exclusively. (× 120 magnification)

favorably changed through hormonal or enzymatic variations. Certainly, in our case there was fundamental derangement of all metabolic processes. The fact that this severe liver derangement was followed by remission appeared to be more than coincidental.

Conclusion

1. This is a case report with autopsy findings of a 41 year old woman with multiple myeloma who, for two years following severe hepatocellular damage, sustained a complete clinical and hematologic remission with concomitant normal total proteins of the blood.

2. The relationship of the remission to the deranged metabolic state resulting from hepatitis is suggested.

Summario in Interlingua

Es reportate le caso—includente le constatationes autoptic—de un femina blanc de 41 annos de etate con un establite diagnose de multiple myeloma in qui, post un curso de progressive deterioration, il occurreva un dramatic remission de duo annos de duration. Durante iste prolongate periodo remissional le patiente exhibiva nulle signos o symptomas. Le conditiones hematologic in le sanguine peripheric e in le medulla ossee esseva normal como etiam le nivello del proteina total in le sero. Un revista del litteratura in re le prognose de multiple myeloma indica que le caso hic reportate es extrememente inusual tanto in le duration como etiam in le completitate del remission.

Le periodo remissional sequeva un sever e quasi mortal episodio de lesion hepatocellular que interrumpeva le curso deteriorante del morbo. Nos discute le character del possibile relation inter le remission e le acute morbo hepatic. Nos examina le datos relative al etiologia del lesion hepatic e arriva al conclusion que ille episodio esseva probabilissimemente un attacco de acute hepatitis seral. Nos postula que un profundemente disturbate stato metabolic causate per le sever morbo hepatic explica possibilemente le suppression del crescentia de cellulas myelomatose durante le periodo del apparente recuperation.

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SCLERODERMA WITH SYMPTOMATIC HEMOLYTIC ANEMIA: A CASE REPORT *

By HUGH FUDENBERG, M.D., *New York, N. Y.*, and M. M. WINTROBE, M.D., F.A.C.P., *Salt Lake City, Utah*

A CASE of hemolytic anemia associated with scleroderma was recently observed at this hospital. In view of the rarity of this association, a brief report seems warranted.

CASE REPORT

A 34 year old clerk, admitted to the Salt Lake General Hospital on February 11, 1954, had been in excellent health until age 27, when he noted pain, swelling and stiffness of the hands, followed by hardening of the involved skin, and malaise, weight loss and asthenia. Over a three year period slow progression of symptoms resulted in increasing limitation of motion. During this time vasomotor symptoms appeared. These consisted of blanching of the distal phalanges of the fingers on exposure to cold, with erythema and paresthesias for 10 to 20 minutes upon returning to a warm environment.

Four years prior to his admission, induration and hyperpigmentation of skin areas of the left arm and over both wrists were noted. In 1950 he entered another hospital, where the diagnosis of scleroderma was established on the basis of clinical findings and a biopsy of the skin. No new symptoms were noted until May, 1953, nine months prior to admission. At this time intermittent fever and malaise appeared. Examination revealed splenomegaly and a normal blood count. Reëxamination in September, 1953, disclosed a moderate anemia. In the ensuing five months the patient received a total of 9 L. of whole blood, each 500 ml. transfusion being followed by a progressively shorter period of abatement of the malaise and weakness. The patient lost 15 pounds during this period.

He had noted no blood loss or easy bruising, and there had been no cardiorespiratory symptoms or dysphagia. No family history suggestive of hematologic disease was elicited.

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From the Department of Medicine, University of Utah College of Medicine, Salt Lake City, Utah.
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Admission physical examination revealed an undernourished, pale, icteric white male with flexion contractures of the fingers of both hands, the overlying skin being hard, tense and shiny. Discrete linear sclerodermatous plaques were present over the left scapula and left arm. In addition, the skin of the forearms was hard and firmly adherent to the underlying tissues. The thickened skin had a light brown appearance which was distinct from the icteric tint. Some reduction in mandibular movement was present. The blood pressure was 115/65 mm. of Hg; pulse, 128; respirations, 20; temperature, 101° F. Both the liver and spleen were palpable 4 cm. below the costal margin. No lymphadenopathy was present.

Laboratory data included volume of packed red cells of 16 c.c. per 100 c.c., hemoglobin of 5.3 gm. per cent, red cell count of 1,400,000 per cubic millimeter, and a mean corpuscular volume of 110 cubic microns, mean corpuscular hemoglobin of

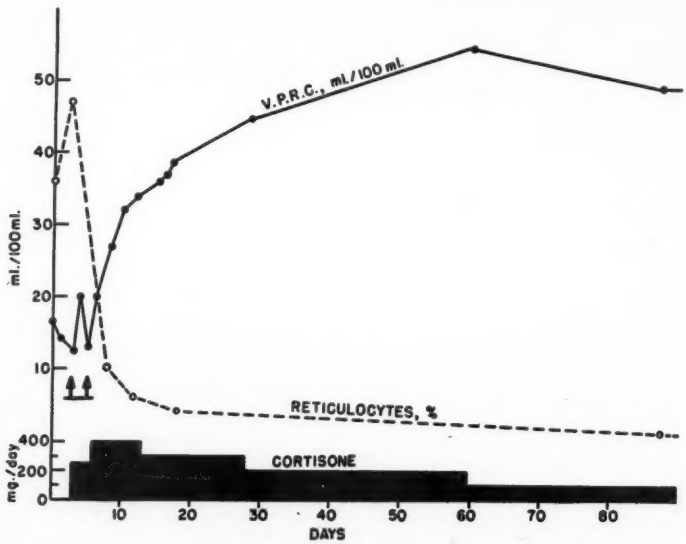

FIG. 1. Effect of cortisone on hemolytic process. V.P.R.C. = Volume of Packed Red Cells. ⬆ = Transfusion (2 units whole blood).

38 micromicrograms, and mean corpuscular hemoglobin concentration of 33%. The icterus index was 25, and the white blood count 14,500 per cubic millimeter, with 59% polymorphonuclear leukocytes, 11% juvenile forms, 3% eosinophils, 16% lymphocytes and 11% monocytes. There were two nucleated red blood cells per 100 white blood cells. The peripheral blood smear showed the red corpuscles to be larger than normal and well filled with hemoglobin, but there were marked anisocytosis and moderate poikilocytosis, polychromatophilia and spherocytosis. Platelets were abundant on smear; the percentage of reticulocytes was 35.8.

Urinalysis revealed no abnormalities. Serum bilirubin was 0.3 mg. % direct, 4.4 mg. % total. Serum proteins totaled 6.1 gm. %, with 3.6 gm. albumin and 2.5 gm. globulin. Zonal electrophoretic analysis * disclosed both a relative and an absolute

* Measured through the courtesy of Dr. Crichton McNeal.

increase in alpha and gamma globulins, without other changes. No cryoglobulins were present. Two preparations for L.E. cells were negative.

Fecal urobilinogen excretion was 320 and 480 Ehrlich units per 100 gm. of stool on two occasions. Warm and cold hemolysins were absent. Spontaneous auto-agglutination of the patient's cells occurred at room temperature, agglutination being present at a serum dilution of 1:4 at 37° C. and 1:64 dilution at 4° C. Trypsinization of the patient's erythrocytes resulted in auto-agglutination at 1:256 serum dilution at 4°, 25° and 37° C. Iso-agglutination titers, using O Rh positive and O Rh negative red cells, did not differ substantially from auto-agglutinin titers.

Skin biopsy sections revealed an atrophic epidermis, beneath which there were masses of hyalinized dermal collagen with chronic inflammatory cells in the interstices.

Hospital Course (figure 1): The volume of packed red cells decreased from 16 to 11.5 c.c. per 100 c.c. during the first three hospital days, while there was a concomitant rise in reticulocytes to 46%. On the third day the patient received two units of whole blood; thereupon the volume of packed red cells increased to 19 c.c. per 100 c.c. The daily administration of 250 mg. cortisone (50 mg. five times daily) was started at this time. The volume of packed red cells decreased to 12 c.c. per 100 c.c. within the next 48 hours, and the patient was given two additional units of

TABLE 1

Date	V.P.R.C. c.c./100 c.c.	Reticulocytes %	Cortisone mg./day	Coombs'		Auto-agglutinin Titer					
				Indirect	Direct	Cold		Room		Warm	
						N*	TR†	N	TR	N	TR
2/14/54	13	35.6	0	‡	‡	1:64	1:256	1:4	1:256	1:4	1:256
3/2/54	39	3.4	300	1:8	2+	1:8	1:32	0	1:32	0	1:32
5/11/54	49	1.4	100	0	+	1:256	1:256	0	1:16	0	1:4
6/8/54	48	1.0	100	0	+	1:64	1:64	0	1:4	0	0

N*—Patient's red cells without trypsinization.
TR†—Patient's trypsinized cells.
‡—Not readable because of spontaneous auto-agglutination.
V.P.R.C.—Volume of packed red cells.

whole blood. The cortisone dosage was increased to 400 mg. daily (100 mg. every six hours). During the next 10 days striking improvement followed, with a rise in the volume of packed red cells to 35 c.c. per 100 c.c., and a decline in reticulocytes to 3.4%. At this time the daily dose of cortisone was reduced to 300 mg. daily. One week later the volume of packed red cells was 39. Auto-agglutination titers at both warm and cold temperatures were now moderately reduced (table 1). The indirect Coombs' test, unreadable at the time of admission because of spontaneous auto-agglutination, was now found to be positive at 1:8 dilution. The direct Coombs' was 2 plus.

Since the patient's discharge on March 4, 1954, the volume of packed red cells has continued to rise even though the cortisone dosage has been progressively decreased. Warm auto-agglutinin activity has continued to decrease. However, the titer of cold auto-agglutinins has increased again despite clinical improvement (table 1). The patient has gained 25 pounds. The range of motion in the affected joints has improved moderately as stiffness has abated. Anorexia, fever, malaise and vasomotor symptoms have vanished. The spleen is no longer palpable. The blood

smear now appears normal. At present he is being maintained on 100 mg. of cortisone daily.

Case Summary: The patient is a 34 year old white male with symmetric thickening of the skin in the hands and forearms, together with two linear plaques of scleroderma. These changes have been present for seven years. In addition, a severe immunohemolytic anemia with both warm and cold auto-agglutinins has developed. Cortisone therapy was accompanied by a striking remission in the hemolytic process, and a decrease in titer of the warm auto-agglutinins.

Discussion

In 1940 Dameshek and Schwartz [1] introduced the designation "symptomatic hemolytic anemia" to embrace those cases of acquired hemolytic anemia displaying an apparent etiologic relationship to certain morbid processes. In their classic report on this syndrome, Singer and Dameshek [2] in 1941 described clear-cut hemolytic processes associated with lymphatic leukemia, Hodgkin's disease, carcinomatosis, sarcoid, dermoid cysts, lymphosarcoma and chronic liver disease. Since then, symptomatic hemolytic anemia has been accepted as a well defined clinical syndrome, and additional cases have been described in association with multiple myeloma,[3] infectious mononucleosis,[4] viremia,[5] carcinoma of the pancreas [6, 7] and kala-azar.[8] Of particular importance is the observation that all signs of increased erythrocyte destruction often disappear following amelioration of the underlying process.[2]

With the present increased interest in the so-called "collagen diseases," many cases previously diagnosed as having merely primary acquired hemolytic anemia have ultimately been recognized as hemolytic anemia of the "symptomatic" type, i.e., secondary to polyarteritis nodosa [9, 10] or to disseminated lupus erythematosus.[11, 12] In the latter condition, symptomatic hemolytic anemia, when carefully searched for, has been noted in 12% or more of various series of cases.[13, 14] Nevertheless, despite the incidence of this syndrome in polyarteritis and lupus erythematosus, no case of hemolytic anemia has as yet, to our knowledge, been reported in association with scleroderma.

It is well known that occasional instances of Raynaud's syndrome are accompanied by high titer cold iso-agglutination and chronic hemolytic anemia.[15, 16] However, the usual cases of scleroderma, with or without Raynaud's phenomena, are not accompanied by these features. Reviews of the past and recent literature [17-21] reveal only a few instances in which scleroderma was associated with anemia of any type. In general, these appear to have been mild hypochromic microcytic anemias.[22] Our patient, on the other hand, displayed all the manifestations of a severe hemolytic anemia of the immunologic variety. Furthermore, treatment with large amounts of cortisone was accompanied by marked amelioration of the hemolytic process. In this patient both warm and cold auto-agglutinins were present. The warm auto-agglutinin titers appeared to vary with the severity of the hemolytic process, irrespective of the cortisone dosage at any given time. Cold auto-agglutinin activity apparently was related to the cortisone dosage level, the titer rising as the dose of cortisone was decreased. These findings are of interest in view of the conflicting statements in the recent literature regarding antibody titer response following effective therapy for immunohemolytic anemia.[24, 25]

Summary

1. A case of scleroderma with symptomatic hemolytic anemia is described. This unusual association is of interest because of its rarity.

2. The hemolytic process in this case was characterized by the presence of both warm and cold auto-antibodies. Cortisone therapy in this patient resulted in marked amelioration of the hemolytic process, and the warm auto-agglutinin titers diminished as the degree of hemolysis decreased. However, the cold auto-agglutinin titers did not appear to be related to the degree of hemolysis, the titers rising when the improved clinical picture permitted a decrease in cortisone dosage.

Summario in Interlingua

Es describite un caso de symptomatic anemia hemolytic secundari a scleroderma. Ben que auto-immunissante morbo hemolytic occurre satis frequentemente in casos de disseminate lupus erythematose e de polyarteritis nodose, usque nunc, secundo nostre informationes, illo non ha unquam essite observate in conjunction con scleroderma.

Le patiente—un masculo de 34 annos de etate—disveloppava splenomegalia 6 annos post le declaration de symptomas systemic attribuibile al morbo fundamental. Brevemente plus tarde sever anemia hemolytic superveniva.

Investigationes serologic revelava "complete" (salin) e "incomplete" auto-anticorpores a temperaturas de inter 4 e 37 C. Le "incomplete" auto-anticorpores esseva demonstrabile per medio del reaction de Coombs e per methodos a trypsinisate erythrocytos.

Therapia a cortisona resultava in un frappante diminution del severitate del processo hemolytic e etiam in un dissociation del calide e frigide configurationes auto-anticorporal. Titros auto-agglutininic a via calide decresceva gradualmente con le attenuation del processo hemolytic. Sed a via frigide le titros auto-agglutininic accresceva. Iste accrescimento esseva apparentemente parallel al reduction gradual del dosage de cortisona post le remission.

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KLINEFELTER'S SYNDROME: A REPORT OF A CASE WITH SOME UNUSUAL FEATURES*

By PHYLLIS C. WALKER, M.D., *Long Beach, California,* and PAUL R. MCCURDY, M.D., *Washington, D. C.*

HYPOGONADISM in the male has long been recognized. However, it is only in recent years, with the use of hormonal assays and testicular biopsy, that a more rational approach to the etiology and treatment of this entity has been utilized. Briefly, hypogonadism has been classified into prepuberal and postpuberal groups, and division has been further aided by determination of the pituitary gonadotropic hormones in the urine. Thus, a hypogonadotropic or

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From the Medical Service of the Veterans Administration Hospital, Seattle, Washington, and the Department of Medicine of the University of Washington School of Medicine.

secondary testicular failure group and a hypergonadotropic or primary testicular failure group are elicited. Testicular morphology correlates with and aids in this differentiation.[1, 2]

Klinefelter, Reifenstein and Albright were among the first to correlate the urinary gonadotropins, testicular biopsy and the clinical picture.[3] In 1942 they published a series of nine cases, now often referred to as Klinefelter's syndrome, characterized by gynecomastia, increased urinary gonadotropins, and hyalinization of the seminiferous tubules without involvement of the Leydig

FIG. 1. The gynecomastia, low temporal hair line, sparse facial and body hair, and trunk obesity are characteristic of the non-eunuchoid group (4) of this syndrome.

cells. Heller and Nelson[4] have modified and enlarged on this so that it may include patients with or without evidence of Leydig cell failure, and absence or presence of gynecomastia; they called the syndrome "puberal seminiferous tubule failure." Thus the constant diagnostic features of this syndrome now include: (1) small, firm testes which microscopically show hyalinization of the seminiferous tubules; (2) azoospermia, and (3) high urinary gonadotropins.

Further subdivision of this syndrome into the eunuchoid, moderately eunuchoid, and non-eunuchoid depends on the amount of androgen produced by the Leydig cells at the time of puberty.

Case Report

A 28 year old, twice-married male was first seen at the Seattle Veterans Administration Hospital in October, 1953, with the chief complaint of intermittent pain in his left breast of 11 months' duration. At age 10 the patient had had mumps with

Fig. 2. Breast tissue (H. and E. × 41), demonstrating the increase in the amount and density of the periductal connective tissue and hyperplasia and bridging of the duct epithelium.

bilateral orchitis, and he believed that his testes had been small since that time. At the time of entry into the service in 1951 he was noted to be somewhat obese but otherwise normal. Shortly after induction he gained 45 pounds rapidly but was able to serve overseas in Korea. After mild trauma to the right breast in May, 1952, he noted gradual enlargement and tenderness. Study at that time showed small genitalia and absence of sperm in the ejaculate. No hormonal determinations were done. The right breast was amputated. He was then essentially well, completing

military service, until November, 1952, when a similar sequence of events occurred in the left breast. Intercourse had taken place one to two times per week and was satisfactory. The patient was allegedly the father of a six month old girl. His body hair had always been sparse, and he had never needed to shave. He had complained of intermittent left flank discomfort since the onset of his gynecomastia; however, he had been able to work as a logger until four months prior to admission, when a knee injury forced him to stop. Increasing weakness and lethargy were prominent the four months prior to entry.

Physical examination on admission (figure 1) revealed an obese male, 68 inches tall. The span was 68½ inches, and height from the floor to the pubis was 34 inches. Obesity was confined primarily to the girdle. The hairline was low on the forehead,

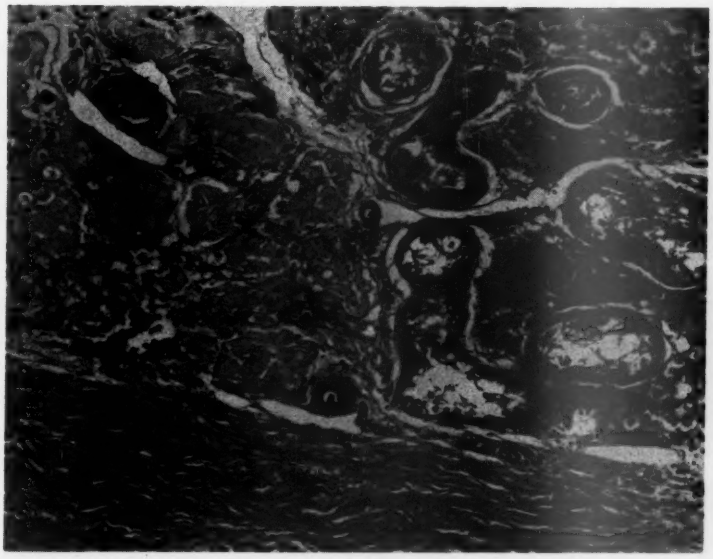

FIG. 3. Testicular biopsy (H. and E. × 144). The tunica albuginea is seen at the bottom. Above this and to the left are atrophied and fibrosed tubules. To the right are seminiferous tubules showing hyalinization of the tunica propria and basement membrane. Only Sertoli's cells are present within the lumina. Leydig's cells are prominent between the tubules.

the beard was practically absent, axillary hair was normal, pubic hair was distributed in the female escutcheon, and absence of all other body hair was noted. The voice tended to crack into a falsetto. The left breast was enlarged and the right absent. The testes were small and soft bilaterally. The penis was small. The prostate gland was normal. The remainder of the examination was within normal limits.

Except for a lymphocytosis with some abnormal forms, which on later admissions reverted to normal, the routine laboratory data were within normal limits. Friedman's test was negative; skull series was negative; protein-bound iodine was normal. Examination of the semen revealed no spermatozoa. The breast was amputated and

a testicular biopsy done (figures 2, 3). The latter was reviewed* and said to be typical of Klinefelter's syndrome. Therapy was started with testosterone propionate, 25 mg. daily intramuscularly for a 30 day trial. On this the patient felt stronger, noted increased growth of body and facial hair, and reported a striking increase in libido.

On re-admission in December, 1953, the physical findings were similar to those found previously except for the operative changes and increased hair growth. Because of the elevated estrogen level and normal gonadotropins, it was decided that further study was needed. The estrogen, 17-ketosteroid and gonadotropin values are summarized in table 1. A retroperitoneal pneumogram done by the presacral route was interpreted as showing a probable tumor in the left adrenal area. Because of these films, the elevated urine estrogen levels, the allegedly late onset of his symptoms and the apparent failure of hormone excretion to be influenced by cortisone or ACTH, the left adrenal area was explored operatively through a left flank incision. The adrenal was normal grossly and microscopically. The postoperative course was uncomplicated. A further hormone study (table 1), done postoperatively, showed 55 mouse uterine units of pituitary gonadotropins in 24 hours, and in an independent laboratory was reported as showing about 200 times normal excretion. Accordingly, it was felt that the suspicion of tumor was unconfirmed and the diagnosis of Klinefelter's syndrome proved as far as was possible. The patient was started on testosterone cyclopentylpropionate, 100 mg. every two weeks, with steadily increasing well being. Four 75 mg. testosterone pellets have just been implanted subcutaneously to serve as long-term maintenance therapy, obviating the need for bi-weekly injections.

TABLE 1

	Pituitary Gonadotropins (Bio-assay) 6–50 Mouse Uterine Units/24 hr.	17-Ketosteroids (Drekter Method) 12–20 mg./24 hr.	Estrogens (Mod. Kober Method) 2–29 mcg./24 hr.
Oct. 1953 No therapy	25	19	38
Dec. 1953 After testosterone for 30 days	30	7.9	31
Dec. 1953 No testosterone for 1 week		14.3	
Dec. 1953 After cortisone 100 mg./day for 6 days Collection started immediately Collection started 24 hr. later		 15.2 8.1	 27 12
Dec. 1953 After ACTH 40U IV day 1 40U IM b.i.d. Days 2 & 3		 16.8	 6.5
Jan. 1954 No therapy	55 (same lab. as above) Calculated 200 times normal (another lab.)		0.20–0.23

* By Dr. Carl Heller, Portland, Oregon.

Discussion

The small testes, which microscopically showed hyalinization of the seminiferous tubules with prominent Leydig's cells, and the clinical picture are compatible with the entity, Klinefelter's syndrome. However, the initial hormone studies, namely, the elevated urinary estrogen and the normal gonadotropins, were puzzling. Heller and Nelson [5] state: "Excretion of estrogen may vary from normal to low but is never increased in amount." Because of the high estrogen level the possibility of a secreting tumor of the adrenal cortex was considered. When a retroperitoneal pneumogram suggested the presence of a mass in the left adrenal area, operative exploration was carried out. Only the left adrenal was examined, but the fact that it was normal and without evidence of atrophy was felt to rule out hyperfunction of the right adrenal. Subsequent estrogen determinations were within normal range. Estrogens were done by the modified Kober method,[6] the accuracy of which as one of the colorimetric methods has been questioned. Pincus [7] states that in nonpregnancy urines the extracts contain large amounts of non-estrogenic chromogens which give an overestimate of the actual estrogen content by the colorimetric reactions usually employed. The gonadotropins when done in another laboratory were markedly elevated. Failure to refrigerate previous samples sent out may have contributed to the discrepancy. Thus it is evident that one of the major difficulties in the diagnosis of an endocrine problem such as this patient presented is accurate and reliable hormone studies.

ACTH and cortisone were administered to determine the effect on 17-ketosteroid and estrogen levels. Cortisone has been shown to suppress strikingly the function of the hyperplastic adrenal cortex, whereas functional adrenal tumors respond less dramatically, if at all, to cortisone administration.[8, 9, 10] It has also been suggested that ACTH will stimulate the 17-ketosteroid production of the normal or hyperplastic adrenal cortex, but not the gland with a tumor.[8] The results in this patient were not consistent, but the failure of estrogens and 17-ketosteroids to fall after administration of cortisone was considered to be an added indication for exploration.

The etiology of Klinefelter's syndrome is unknown, but it has been speculated that it is a congenital abnormality which becomes manifest at or after the time of puberty. The relationship of mumps orchitis, of which this patient gives a history, to the testicular failure can only be surmised. Orchitis is rare but not unknown prior to puberty.[11] In a study of the histopathology of acute mumps orchitis Gall [12] describes focal inflammatory changes in the tubules of the testis which may go on to tubular atrophy and hyalinization. However, he concludes that complete testicular atrophy and sterility would be a rare occurrence following mumps orchitis because of the spotty distribution of the lesion.

Summary

A case of Klinefelter's syndrome has been reported, with a brief review of this entity and of some of the difficulties encountered in the interpretation of hormone values.

Acknowledgment

The authors wish to thank Dr. John L. Bakke for his helpful suggestions and criticism.

SUMMARIO IN INTERLINGUA

Le syndrome de Klinefelter es characterisate per parve e firme testes con hyalinisation del tubulos, azoospermia, e alte nivellos de gonadotropina urinari.

Nos presenta un caso del syndrome de Klinefelter con le sequente tractos inusual: historia de parotiditis con orchitis bilateral al etate de 10 annos, presumption de paternitate, initialmente elevate nivellos del estrogenos urinari con nivellos normal del gonadotropinas urinari, e absentia de evidente effectos modificatori de ACTH e cortisona super le hormones urinari. Quando le pneumogramma retroperitoneal revelava le presentia de un massa sinistroadrenal, un exploration negative esseva executate.

Altere post-operative studios hormonal indicava un grandemente augmentate excretion de gonadotropinas pituitari. Isto—insimul con le constatationes clinic e pathologic—pote esser considerate como un confirmation del diagnose de syndrome de Klinefelter.

Nos discute le causas de diagnoses erronee in iste condition. Nos conclude que penosemente exacte studios hormonic es indispensabile in le investigation de iste genere de problema endocrinologic.

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VENOUS AND ARTERIAL THROMBOSES IN ASSOCIATION WITH CARCINOMA OF THE PANCREAS *

By DAVID BUTTROSS, JR., M.D., *Lake Charles, Louisiana,* and JOHN SALATICH, M.D., *New Orleans, Louisiana*

TROUSSEAU [1] in 1865 appears to have been the first to mention an increased incidence of thrombophlebitis in patients with carcinoma. Only recently, however, has the rather striking incidence of venous thrombosis and pulmonary embolism associated with cancer of the pancreas been given much attention in the literature.[2–18] In only one of these articles [13] is mention made of arterial as well as venous thromboses in cases of pancreatic carcinoma. Although there has been considerable speculation,[3, 4, 10] the cause of this increased susceptibility to thrombo-embolic phenomena has not been determined.

We have observed numerous cases of carcinoma of the pancreas in which venous thromboses and pulmonary embolism played an important role in the terminal picture, but the case to be reported is the only one we have seen which first presented with a picture of occlusive disease of the arteries and veins of the extremities.

CASE REPORT

On July 3, 1952, a 55 year old white male electrician presented himself in the Outpatient Department of Charity Hospital with a chief complaint of severe pain in the fingers of the left hand which had begun only a few hours before. The patient stated that previous to this time he had been in excellent health.

Examination showed moderate blueness of the fingers of the left hand but no alteration of skin temperature. Brachial and radial pulses were of good and equal volume on the two sides. Aminophylline was given intravenously, with questionable benefit, and the patient was sent home.

Four days later he returned to the hospital and was admitted. He stated that since the onset the finger tips of the left hand had remained blue, cold and painful. At this time the left radial pulse was still palpable and of good volume, but there was definite decrease in skin temperature of the left hand. General physical examination disclosed no striking abnormalities except an enlarged liver which could be felt three fingerbreadths below the rib margin and which was firm in consistency. (The patient admitted a moderate alcohol intake over a number of years.) Blood pressure was 125/70 mm. of Hg, equal in the two arms. Routine laboratory tests were normal with the exception of a leukocyte count of 12,000, with 84% neutrophils. X-rays of the chest and cervical spine were normal. An electrocardiogram was well within normal limits. Three stellate ganglion blocks with procaine were performed on successive days, with temporary relief of the pain after each one but without effect on the cyanosis of the fingers. On July 11 the left stellate and first and second thoracic sympathetic ganglia were removed. Following the operation the patient experienced no more pain until his discharge on July 18, but cyanosis of the finger tips persisted. Discharge diagnosis was spasm of small arteries in the left upper extremity of unknown etiology.

On July 17, only a day after discharge, the patient again experienced severe pain in the left hand associated with coldness and a bluish pallor. He was readmitted for further study.

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From the Department of Medicine, Louisiana State University School of Medicine, and Charity Hospital, New Orleans, Louisiana.

Reëxamination disclosed no new findings, nor was additional laboratory work revealing. Priscoline and other vasodilators were given without effect, and large doses of analgesics were required to relieve the pain.

About August 1 it was noted that the volume of the left radial pulse and of the left brachial below its midportion were greatly decreased. On August 2 the patient began to complain of pain and swelling of the lower extremities. Examination showed moderate pitting edema and patchy bluish erythema over both feet and legs. There was no palpable evidence of venous thrombosis, and the pulses in the femoral, popliteal, posterior tibial and dorsalis pedis arteries were of good volume on both sides.

At this time studies were instituted to determine whether the blood was hypercoagulable, or whether there was any abnormality of the platelets. Coagulation time by a sensitive modification of the Lee-White technic was normal, and platelet counts varied between 200,000 and 300,000. Bone marrow studies disclosed no abnormalities.

Because of the probability of venous thromboses in the legs, anticoagulant therapy with heparin and Dicumarol was instituted and maintained for several weeks. During this period, in which prothrombin time was carefully maintained within the "therapeutic level," the patient experienced two definite episodes of pulmonary infarction. On August 10 he experienced a sudden pain in both legs, which were found to be cold, cyanotic and pulseless. After bilateral lumbar sympathetic block the pulse could be felt in the right femoral artery but not in the left. Left lumbar sympathectomy resulted in no improvement, and gangrene of the left foot and lower portion of the leg developed, necessitating amputation. The pathologist reported that the changes in the vessels of the amputated extremity were compatible with Buerger's disease, but this opinion did not seem to fit into the clinical picture of sudden occlusion of large vessels. No evidence of atherosclerosis was noted in the arteries of the amputated extremity. The patient was discharged on October 9 in relatively good condition but with persistent, annoying pain in the fingers of the left hand, the tips of which now presented some evidence of incipient dry gangrene.

On October 26 he was re-admitted with another acute episode of pulmonary infarctions. At this time physical examination revealed a large, stony-hard mass in the epigastrium which moved with respiration. Only at this time was the real etiology of the thrombo-embolic phenomena apparent to us. Conditions previously considered had been Buerger's disease, arterial embolism from plaques of aortic atherosclerosis, arteriosclerosis obliterans of an unusual type, and essential thrombophilia.

On this admission there were glycosuria and moderate hyperglycemia.

Early in November, signs of phlebothrombosis developed in the left arm; later he began having pain, swelling and coldness of the right lower extremity, followed by gangrenous changes of the toes. On November 21 jaundice was noted, which rapidly increased in degree. On November 26, at the patient's request, he was discharged.

On December 25 he was re-admitted, complaining of weakness and severe pain in the abdomen and extremities. He had lost a great deal of weight, and the mass in the upper abdomen had increased in size. The first, second and third toes of the right foot and the distal phalanges of the second and third fingers of the left hand were gangrenous. He died on January 2, 1953.

Autopsy revealed a ductal adenocarcinoma of the head of the pancreas with metastases to the liver, lungs and periaortic nodes. There were bilateral pulmonary infarcts of various ages, and multiple small infarctions of the left kidney. There was only slight aortic atherosclerosis, and no evidence of significant disease of the large branches of the aorta. The small arteries of the extremities were not examined, but those of the visceral organs showed no pathologic changes.

Summary

A case is reported of carcinoma of the head of the pancreas which presented first with evidence of occlusive disease of the small arteries of one hand, of sudden onset. Only after the patient had developed numerous episodes of arterial and venous thrombosis and had been subjected to many sympathetic blocks, sympathectomy and one amputation did the discovery of a mass in the abdomen lead to the correct diagnosis.

The case is reported principally because of the apparent rarity of arterial thrombosis in cases of cancer of the pancreas, but it also may serve to emphasize the fact that vascular thrombosis may antedate the other common and more familiar symptoms of pancreatic cancer.

Summario in Interlingua

Le accrescente frequentia de thromboses venose e embolismo pulmonar in association con carcinoma del pancreas es un facto ben cognoscite.

Nos ha vidite numerose casos de carcinoma del pancreas in que thromboses venose e embolismo pulmonar habeva un importante rolo in le stato terminal, sed le caso que forma le thema del presente reporto es le sol in nostre experientia que comenciava per exhibir le symptomatologia de morbo occlusive del arterias e venas del extremitates. In iste caso le discoperta de un massa intraabdominal suggereva le correcte diagnose solmente post que le patiente habeva disveloppate numerose episodios de thromboses arterial e venose e post que ille habeva essite subjicite a multe blocos sympathic, a sympathectomia, e a un amputation.

Le caso es reportate principalmente a causa del apparente raritate de thromboses arterial in casos de carcinoma del pancreas. Illo va etiam servir a sublinear le facto que thrombosis vascular pote preceder le altere commun e melio-cognoscite symptomas de carcinoma pancreatic.

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EDITORIAL

DE MOTU INTERLINGUAE

WITH this issue of the ANNALS OF INTERNAL MEDICINE an abstract of each original article appears in Interlingua. It is hoped that by this device those of our readers who do not read English fluently will be enabled quickly to evaluate each paper and so determine whether it merits a laborious study or translation. Also, provided our summaries are adequate, it will permit readers who are not familiar with English to gather the essence of each article in capsule form.

Because Interlingua is new, many of our readers will probably be interested to know something about its origin, its nature, its aims and present status. The following brief outline is therefore submitted.

Interlingua is a scientifically constructed language which aims to play the same rôle in overcoming language barriers as did Latin until the end of the 17th century. When William Harvey in 1628 published his epochal researches on the circulation of the blood, "De Motu Cordis," he wrote in Latin. He did so because it was then the standard "interlingua" of western civilization and was immediately intelligible to the scholars, philosophers and scientists of every European country.

As is well known, Latin, despite its great advantage as an interlingua, has since then gradually declined so that it has now disappeared as a living language from the world of science. It has been replaced by a babel of mutually incomprehensible modern languages which tend to divide rather than to unite current scientific thinking. The Latin vocabulary still lingers on in official nomenclature and terminology and still furnishes the raw material out of which new scientific terms are constantly coined. But, as a functioning language it is dead.

Much as we may regret the loss of this universal language, few of us would now lift a finger to bring it back. The reason is all too obvious. Latin is too difficult and there is now no time in modern scientifically oriented curricula for the many years of study needed to master its intricacies. Yet our rapidly contracting world needs more than ever some common medium of communication.

If Latin is beyond resuscitation, what can take its place?

A National Language for International Use: Those who have not reflected deeply on the problem often suggest that a national language (usually their own) should be "selected." Unfortunately there is very little in international linguistic history to indicate that any *one* language could be selected to the exclusion of others. In world medical congresses, in the League of Nations and now in the United Nations the most that has been achieved is a rather awkward selection of three or four languages, never the selection of a single language. The history of the regional use of national languages in

the rôle of international languages indicates their dependence on the ebb and flow of political events. The scientific world needs a standard neutral language which will be unaffected by the rise and fall of empires and their transient cultural predominance.

The International Vocabulary: Running counter to these divisive linguistic currents to which we have alluded there is on the other hand a strong unifying force which is rapidly gaining momentum and which is inextricably bound up with the rise and expansion of Western civilization. The driving force behind this expansive cultural movement is what is popularly called "science" and the basic language of science is unquestionably the Graeco-Latin vocabulary.

The International Vocabulary also includes a vast body of non-technical words (probably 100,000 or more) which, while differing somewhat in form and spelling, are common to English, French, Spanish, Italian and Portuguese. These are almost all of Latin origin and are therefore also familiar to educated Germans, Scandinavians and others who have a grounding in Latin together with a knowledge of either English or one of the Romance languages. To a much lesser extent, and mainly in the field of technical and scientific terminology, many of these words are diffused in the Slavic languages and in the languages of the near and far East.

No secondary or competitive international vocabulary exists which could present a rival claim. The great non-occidental culture languages such as Arabic, Chinese, Hindustani, Japanese, Malay and Russian have nothing whatever in common as a group except those words which they have already accepted from Graeco-Latin sources.

It would thus seem that the international vocabulary, if properly abstracted and defined, might furnish the basis for a workable international language. Interlingua claims to be just that: a properly defined abstract of a living international vocabulary.

Constructed International Languages: The idea of creating an international language is by no means new. It goes back at least 300 years. Of the many schemes proposed only two have attained any degree of recognition, namely Esperanto (and its reformed version Ido) and Occidental. Of these, Esperanto especially has tended to operate at sub-scientific levels and to be the organ of a cult of well meaning but futile internationalistic idealism. Unfortunately, the word "Esperanto" has come to be synonymous with the general idea of an international language, and, because of its grotesque appearance it is too often assumed that the idea itself is unsound. Who, for instance, reading the Esperanto sentence "La gepatroj amas siajn bonajn kaj fidelajn knabinojn." * would be moved to write a scientific paper in that language? and if he did, who could read it?

* (The Interlingua rendering of this sentence is "Le parentes ama lor bon e fidel pueras.")

The Background of Interlingua: In 1919 the International Research Council stimulated the American, British, French, and Italian Societies for the Advancement of Science to appoint committees to investigate the possibility of supplying a neutral scientific language for use in international scientific communications. The project languished except in the U. S. A., where, under the direction of the International Auxiliary Language Association, a systematic exploration of the problem was begun in 1924. Numerous linguists, philologists, and scholars in related fields conducted a painstaking study of the problem from 1924 on. In 1951 a dictionary of approximately 27,000 standardized international words was published with a grammar by means of which the vocabulary could be operated.

This work is unique in the field of interlinguistics since it is based on meticulously exact scholarship from beginning to end. The resulting vocabulary contains nothing artificial or invented, and therefore represents the recovery of an already existing language and *not* the invention of a new one.

Methods of Extraction and Standardization: Despite what has been said regarding the identity of the word material of the international vocabulary, the task of standardizing it is a formidable one. If anyone doubts this, let him compare parallel texts in English, French, Italian, Spanish, and Portuguese! Nevertheless, the task has been accomplished.

A word is eligible for inclusion in the vocabulary of Interlingua if it is present in three of the four languages under scrutiny (English, French, Italian and Spanish-Portuguese). Where the form of the word is identical it is adopted without change. For instance, the English word "present" is identical in all five languages under consideration and appears in Interlingua as "presente." However, where the form of a word varies from language to language, the "nearest documented or hypothetical ancestor" of the word is chosen. Thus, for English "school," where the following national forms also exist: école, scuola, escuela and escola, the Latin "schola" is automatically selected. Its meaning is clear to us from such words as "scholarship," "scholastic," "scholar," etc.

Interlingua Grammar: Only those grammatical features common to all the source languages are retained. This automatically reduces the grammar to the minimum which is found in English. Thus, there is no agreement of adjectives with nouns, no grammatical gender, no subjunctive, and no inflected conjugations. Word order follows the general pattern of the Romance languages.

It would, of course, be possible to operate the international vocabulary with a variety of grammars; even an artificial grammar such as that of Esperanto could be used, but as can be seen from the Esperanto text above, nothing much would be gained thereby.

The Qualities of Interlingua: Interlingua has the general appearance of a natural Romance language freed from dialectical peculiarities. In the last two years I have shown it to speakers of all the Romance languages. Without exception they read it fluently and with complete understanding. Each assumed that it was the one Romance language with which he was not familiar. None guessed that it was a constructed language.

English speakers with normal linguistic ability and training do almost equally well when reading technical material in their own field. The same holds true for speakers of German. Of course this ease of comprehension depends on the previous knowledge of language which all well educated persons possess. Unfortunately there are a few intelligent and well educated people who seem to be "linguistic cripples" and who have difficulty in expressing themselves clearly even in their own mother tongue. To these neither Interlingua nor any foreign language will appeal.

The Range of Interlingua: Interlingua is comprehensible to the intellectual leadership of approximately half a billion people. Thus all of Western Europe, Great Britain and her Empire, the French and Portuguese Empires, and all of North and South America constitute a vast area of the world where doctors and scientists can be addressed directly in Interlingua. To this may be added the governing classes of all of Africa south of the Sahara Desert.

No other language, whether natural or artificial, possesses anything like this range of comprehensibility. Thus if an Interlingua text were translated into English, Spanish, Portuguese, Italian, German or any other national language, its range of comprehensibility would immediately be greatly *restricted.* Because of this, Interlingua can immediately be put to practical use in the field of mass-communication.

The Current Application of Interlingua: Interlingua seeks only to supplement whatever devices already exist to overcome language barriers. It does not wish to encroach on the use of national languages where these have an established function in international communications. It welcomes the I.B.M. multiple translation system at scientific congresses and regards itself as complementary to it at the level of the written word.

Since its introduction three years ago, Interlingua has found a useful rôle in scientific publications. Under the direction of Science Service, a monthly bulletin "Scientia International" is now entering its third year of publication. "Spectroscopia Molecular" is another bulletin, devoted to a highly specialized field. The following medical journals are either using, or plan to use Interlingua translations of summaries of their original articles: *American Heart Journal, American Journal of the Medical Sciences, American Journal of Psychotherapy, Annals of Internal Medicine, Blood, Circulation, Clinical Orthopedics, Archivos Peruanos de Patología y Clínica, Diabetes, Journal of Dental Medicine, Pediatrics* and the *Quarterly Bulletin*

of the Seaview Hospital. Numerous other journals in this country and in Europe and South America appear to be interested.*

Interlingua grammars in German and French have been published in Switzerland for European consumption and Spanish and Italian editions are in preparation. At the Second World Congress of Cardiology (Washington, D. C., 1954), abstracts of all papers (amounting to 85,000 words) were printed in Interlingua. Also in 1954 at the International Conference on Hematology in Paris, the presidential address was printed in Interlingua. A course in Interlingua is scheduled at New York University.

Reviewing the above, it seems to us that Interlingua has found a useful place in the medical journals of the western world. We think it is here to stay. How far it will go to recapture the function which Latin exercised in Harvey's day remains to be seen. We at least seem to have a working model of a new form of Latin which will aid in the circulation of medical information. American doctors would welcome the introduction of Interlingua summaries in European and South American Medical Journals.

JOHN LANSBURY, M.D., F.A.C.P.

* Inquiries regarding Interlingua should be addressed to Interlingua Division of Science Service, 80 East 11th Street, New York 3, N. Y.

REVIEWS

Clinical Neurology (in three volumes). Edited by A. B. BAKER, M.D., Professor and Director, Division of Neurology, University of Minnesota Medical School; by 65 authors. 2023 pages; 18 × 26 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1955. Price, $60.00.

This three-volume work on clinical neurology contains sections written by 65 collaborators. The first volume is concerned with the neurological examination, diagnostic methods, cerebral localization, cerebral tumors and vascular diseases. The second volume deals with infections, toxins, demyelinating diseases and extrapyramidal systems, as well as the brain stem and spinal cord. The last volume continues with the spinal cord, muscular and peripheral nerve affections, congenital disturbances, and the neurological complications of systemic diseases. There are additional chapters on neurologic rehabilitation and the genetics of neurological diseases. This accumulation of the material necessary for the practice of medical neurology at one source is a masterful attempt to fill a need which has long been apparent. It has resulted in 1960 pages of factual and valuable current information. At times detail is lacking; however, each chapter is followed by an extensive bibliography of the original material, enabling the interested reader to find the details he desires. The index is adequate and useful and the print is clear.

This work is a very desirable addition to the library of any who are engaged in the practice of neurology, neurosurgery, or psychiatry. In addition, it will prove useful as a reference work for all other physicians.

C. V. B.

Fibrosis of the Liver in West African Children. Medical Research Council Special Report No. 285. By J. H. WALTERS and J. C. WATERLOW. 98 pages; 15 × 24.5 cm. (paper-bound). Her Majesty's Stationery Office, London. 1954. Price, 8s. 6d. net.

The natives living along the Gambia River in West Africa are subjected by the nature of their primitive agriculture to annual cycles of severe fasting and malnutrition. Enlargement of the liver is present in almost all of the children in this region by the age of two years. This monograph reports a study mainly of liver biopsies in the attempt to establish the etiologic factors in the pathogenesis of the hepatic lesions.

The major portion of the report deals with the pathologic anatomy of the liver and detailed histologic examinations are described, with numerous plates. The authors distinguish two types of mild periportal fibrosis occurring in most of the livers. They differentiate the lesions seen from the massive fatty livers of Kwashiorkor by the relatively minimal fat content of their cases. In Kwashiorkor fat content reaches 30%, whereas there was no more than 10% fat in any of their cases. In addition, they point out that periportal fibrosis is not a feature of Kwashiorkor.

The pathogenesis of the lesions is discussed at length, and, as with all purely anatomical studies taken at a single point of time (the serial biopsies done in a number of patients over a few months showed no significant changes) is highly speculative. Since no single lesion seems to explain the histologic picture the authors suggest a dual mechanism based on the fact that almost all the children are infected with malaria by the age of two years, and the above mentioned cycles of malnutrition. They feel that the malarial infestation of the liver increases the susceptibility of that organ to nutritional insult.

Some analyses of plasma cholinesterase content are reported, and they are somewhat lower than the levels for European children. There is inverse correlation with the clinical condition of the children, but, as the authors observe, there is no known function of this enzyme in plasma. Its relation to the picture is, therefore, obscure.

This monograph is an excellent addition to the growing documentation of our lack of understanding of the liver. It suggests the manifold reactions of this organ to subtle and as yet unidentified factors in the environment.

S. P. B.

Diagnostic Laboratory Hematology. By GEORGE E. CARTWRIGHT, M.D., Associate Professor of Medicine, College of Medicine, The University of Utah, Salt Lake City, Utah. 104 pages; 14 × 22 cm. Grune & Stratton, Inc., New York City and London. 1954. Price, $3.00.

This concise, well written and practical manual should fulfill the need for which it was written—to provide the essential details for the performance of procedures commonly used by medical students, house staff officers and practicing physicians for the diagnosis of hematologic disorders. The author presents but one method for each of the numerous procedures mentioned and states it to be the most practical for the examination in question, in his experience. The reader is referred to other more involved standard texts for collateral reading.

The appendix, concerning the preparation of most commonly used laboratory reagents, is a novel and invaluable addition to an already important monograph that should find its way into the library of many young physicians as well as students.

J. B. W.

Cancer of the Thyroid: A Monograph for the Physician. By JOHN DEJ. PEMBERTON, M.D., Emeritus Member, Section of Surgery, and B. MARDEN BLACK, M.D., Section of Surgery, Mayo Clinic, Rochester, Minnesota. 46 pages; 16 × 24 cm. (Paper-bound.) Ninth of a series on the early recognition of cancer, published by the American Cancer Society, New York. 1954. Free.

The American Cancer Society continues to present from time to time summaries of the current concepts of diagnosis and treatment of various primary malignancies in the form of concise and well written monographs prepared by authorities in the field. The present monograph is the ninth of the current series and is no exception since it attempts to summarize current thinking in the confusing field of thyroid malignancy.

Considerable space is given over to a discussion of the relationship between cancer and nodular goiter with the final decision favoring the surgical removal of all such "cold" nodules.

The remainder of the monograph discusses diagnosis, types of malignant lesions from the pathological point of view, therapy with emphasis on surgical means, and ends with prognosis. It is unfortunate that the newer means available for stimulating metastatic thyroid tissue into picking up radioactive iodine (i.e., thiouracil, thyroid stimulating hormone) are passed over.

Both color and black and white illustrations are of value in the understanding of the thyroid cancer problem and are included in the text. A short but pertinent bibliography is appended.

The monograph should be read, if only for review, by the surgeon as well as the internist, for thyroid cancer should lend itself to early recognition by the alert and informed physician.

J. B. W.

Current Concepts in Digitalis Therapy. By BERNARD LOWN, M.D., Formerly Assistant in Medicine, Peter Bent Brigham Hospital, and SAMUEL A. LEVINE, M.D., Clinical Professor of Medicine, Harvard Medical School. 164 pages; 12.5 × 18.5 cm. Little, Brown and Company, Boston, Mass. 1954. Price, $3.50.

The administration of digitalis in adequate therapeutic amounts and without producing untoward toxic effects may present many problems. It is important for the practitioner of medicine to understand the principles involved in the proper employment of this drug.

In this book are presented the "current concepts" of digitalis therapy under such chapter headings as: The Action and Clinical Use of Digitalis, Digitalis Intoxication, Electrolytes and Digitalis, Relation of Potassium to Digitalis Intoxication, and Paroxysmal Atrial Tachycardia with Block. The text is clear, concise, and well documented with an excellent bibliography of 329 references. This book will serve as a useful source of information for resolving many problems involved in the proper use of digitalis and in treating digitalis intoxication. There is also included a discussion of a "digitalis tolerance test" involving the use of acetyl strophanthidin. "The amount of drug necessary for a therapeutic or toxic end point determines whether digitalis is to be used and the approximate dosage for optimal effect." This test is certainly not without danger and should rarely be necessary. As the authors point out, "Our experience has impressed us both with its great value and its potential danger. Its use is justified only in the most carefully selected cases."

L. S.

Emotions and Bodily Changes: A Survey of Literature on Psychosomatic Interrelationships, 1910–1953. 4th Ed. By FLANDERS DUNBAR, M.D., Med. Sc.D., Ph.D. 1,192 pages; 16 × 24 cm. Columbia University Press, New York. 1954. Price, $15.00.

This newest (fourth) edition of Flanders Dunbar's well known work on the psychosomatic disorders, bears the sub-title "A Survey of Literature on Psychosomatic Interrelationships, 1910–1953." It is a very substantially enlarged collection of abstracts of parts or the whole of articles, which the author feels have made a definite contribution, "positive or negative," in this complex field, up to 1953. The pages given to bibliography alone in this edition are 263, as compared to 131 in the second edition, published in 1938, showing the greatly increased amount of investigation which has gone on since that time.

She says in the introduction "We have reached a point where progress in the specialties themselves is being blocked by lack of understanding of the relationships between them," which seems to define much of the difficulty in the field of psychosomatic medicine.

In Part II, the Organs and Organ Systems, several divisions have been much enlarged, both as to the author's comment on emotional problems associated with dysfunction in any particular organ or system, and as to the greatly increased number of references and partial abstracts of investigative work being done. In the chapter on genito-urinary and gynecological difficulties, fresh emphasis is placed on the view that "Disorders of the genito-urinary tract are as firmly rooted in the child-parent relationship as are disorders of the metabolic and gastro-intestinal systems." And, "Certain leading gynecologists, although fundamentally ignorant of or opposed to, psychoanalysis, are none-the-less reaching the conclusion on the basis of their own observations and experience, that the majority of gynecological problems are psychosomatic."

In the section on cardiovascular disease, in connection with the increase of coronary artery disease in young adults (especially males) some excellent articles are

cited of work done on personality studies of young adults developing this disease, and also studies of sociological factors which seem to be operating in this country as a factor in this increase.

A good many references cited seem to represent very fragmentary studies of small parts of a problem, and usually the author introduces them as such. As she herself states in the introduction, "it must be borne in mind that this work is essentially a bibliography. Its value is not in the thorough presentation of the contributions made by each specialty to the problem in hand, but instead in its general indication of the type of material we have, where it is to be found, and where it is particularly lacking."

As such a guide to further more thorough reading in the many different areas of investigation going on in psychosomatic medicine, this book seems a valuable volume for every medical library.

H. W. N.

Gestation: Transactions of the First Conference, March 9, 10, 11, 1954, Princeton, N. J. Edited by LOUIS B. FLEXNER, M.D. 238 pages; 16 × 23.5 cm. Sponsored by the Josiah Macy, Jr. Foundation, New York. Published by Corlies, Macy & Co., Inc., New York, N. Y. 1955. Price, $5.00.

These transactions are the result of the first conference on gestation under the able chairmanship of George B. Wislocki, composed of the foremost anatomists, physiologists, and scientists in the fields of biochemistry, embryology, obstetrics, and gynecology who are interested in placentation. The data were presented in three parts, namely, the functional rôle of the placenta (Louis B. Flexner), problems of sugar transport in the placenta of the ungulate (A. St. G. Huggett), and the comparative anatomy and histology of the placental barrier (Emmanuel C. Amoroso). Methods of transfer were discussed and it was the conclusion that these transfers occur by four mechanisms: (1) diffusion, (2) active cellular transfer, (3) pinocytosis, (4) pathological leaks, and possibly more, not yet known.

Grosser's classification of the four major types of placental membranes was thoroughly discussed and it was the general opinion that for the uninitiated it was a satisfactory classification but at the scientific level it had several drawbacks. It was not thought advisable, however, to enlarge upon this particular classification at this particular conference.

The recent knowledge gained by the electromicroscope in the histological appearance and function of the placenta was discussed.

These transactions are recommended to anatomists, physiologists, and research scientists who are interested in placentology of the human and of the lower animals and to anyone interested in fundamental investigations of the placental membranes in all species of animals.

D. F. K.

BOOKS RECEIVED

Books received during May are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Annual Review of Medicine. Volume 6, 1955. DAVID A. RYTAND, Editor, Stanford University School of Medicine; JOHN ANDERSON, Associate Editor, Stanford University School of Medicine. 459 pages; 23.5 × 15.5 cm. 1955. Annual Reviews, Inc., Stanford, California. Price, $7.00.

The Behavior of Pulmonary Tuberculous Lesions: A Pathological Study. By E. M. MEDLAR, Chief Pathologist, Division of Tuberculosis, New York State Department of Health, Hermann M. Biggs Memorial Hospital, Ithaca, New York, etc. 244 pages; 26 × 17.5 cm. 1955. Monograph appeared as a supplement of the March, 1955 issue of the *American Review of Tuberculosis,* 1790 Broadway, New York. Price, $2.50, clothbound; $1.50, paper-bound.

Bickham-Callander Surgery of the Alimentary Tract. Volumes I, II and III. By RICHARD T. SHACKLEFORD, M.D., Assistant Professor of Surgery, Johns Hopkins University School of Medicine; assisted by HAMMOND J. DUGAN, M.D., Assistant in Surgery, Johns Hopkins University School of Medicine. 2,575 pages (total, three volumes); 26 × 18.5 cm. 1955. W. B. Saunders Company, Philadelphia. Price, $60.00 per set.

Bone and Joint X-Ray Diagnosis. By MAX RITVO, M.D., Assistant Clinical Professor of Radiology, Harvard Medical School, etc. 752 pages; 26.5 × 18 cm. 1955. Lea & Febiger, Philadelphia. Price, $20.00.

Cardiac Auscultation, Including Audio-visual Principles. By J. SCOTT BUTTERWORTH, M.D., Associate Professor of Medicine, New York University Post-Graduate Medical School; MAURICE R. CHASSIN, M.D., Assistant Professor of Clinical Medicine, New York University Post-Graduate Medical School; and ROBERT MCGRATH, M.D., Associate Professor of Clinical Medicine, New York University Post-Graduate Medical School. 111 pages; 24 × 16 cm. 1955. Grune & Stratton, New York. Price, $4.50.

Cerebral Vascular Diseases: Transactions of a Conference Held under the Auspices of The American Heart Association, Princeton, New Jersey; January 24–26, 1954. IRVING S. WRIGHT, Chairman; E. HUGH LUCKEY, Editor. 167 pages; 26 × 17.5 cm. 1955. Published for The American Heart Association by Grune & Stratton, New York. Price, $5.50.

Cornell Conferences on Therapy. Volume 7. Edited by HARRY GOLD, M.D., Managing Editor; DAVID P. BARR, M.D., MCKEEN CATTELL, M.D., FRANK GLENN, M.D., and GEORGE READER, M.D. 264 pages; 21.5 × 14.5 cm. 1955. The Macmillan Company, New York. Price, $4.50.

Fettleibigkeit. By PROF. DR. HERMANN BERNHARDT. 231 pages; 24.5 × 16 cm. 1955. Ferdinand Enke Verlag, Stuttgart. Price, Geheftet DM 21.; ganzleinen DM 23.20.

Fifty Years in Group Psychotherapy: Commemorating the Pioneering of Joseph Hersey Pratt, M.D., 1905–1955. Edited by JOSEPH H. KAPLAN, M.D., PAUL E. JOHNSON, Ph.D., and HALDEAN S. LINDSEY, S.T.M. Pages not numbered; 23 × 15 cm. (paper-bound). 1955. The New England Medical Center, Boston. Price, $1.00.

The Hypophyseal Growth Hormone, Nature and Actions: International Symposium Sponsored by the Henry Ford Hospital and Edsel B. Ford Institute for Medical Research, Detroit, Michigan and Held at the Hospital October 27, 28, 29, 1954. Editors: RICHMOND W. SMITH, JR., M.D., Physician-in-Charge, Division of Endocrinology, Henry Ford Hospital, Detroit; OLIVER H. GAEBLER, M.D., Head, Biochemistry Department, Edsel B. Ford Institute for Medical Research, Detroit; and C. N. H. LONG, M.D., Sterling Professor of Physiology, Yale University School of Medicine, New Haven. 576 pages; 24 × 15.5 cm. 1955. The Blakiston Division, McGraw-Hill Book Company, Inc., New York. Price, $12.00.

Mental Health and Human Relations in Industry. Edited by T. M. LING, M.A., D.M. (Oxon.), M.R.C.P., Medical Director, Roffey Park Institute of Occupational Health and Roffey Park Rehabilitation Centre, Horsham, Sussex, England; supplementary introduction by THOMAS A. C. RENNIE, M.D., Professor of Psychiatry (Social Psychiatry), Cornell University Medical College, New York, N. Y. 265 pages; 22.5 × 14 cm. 1955. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $6.00.

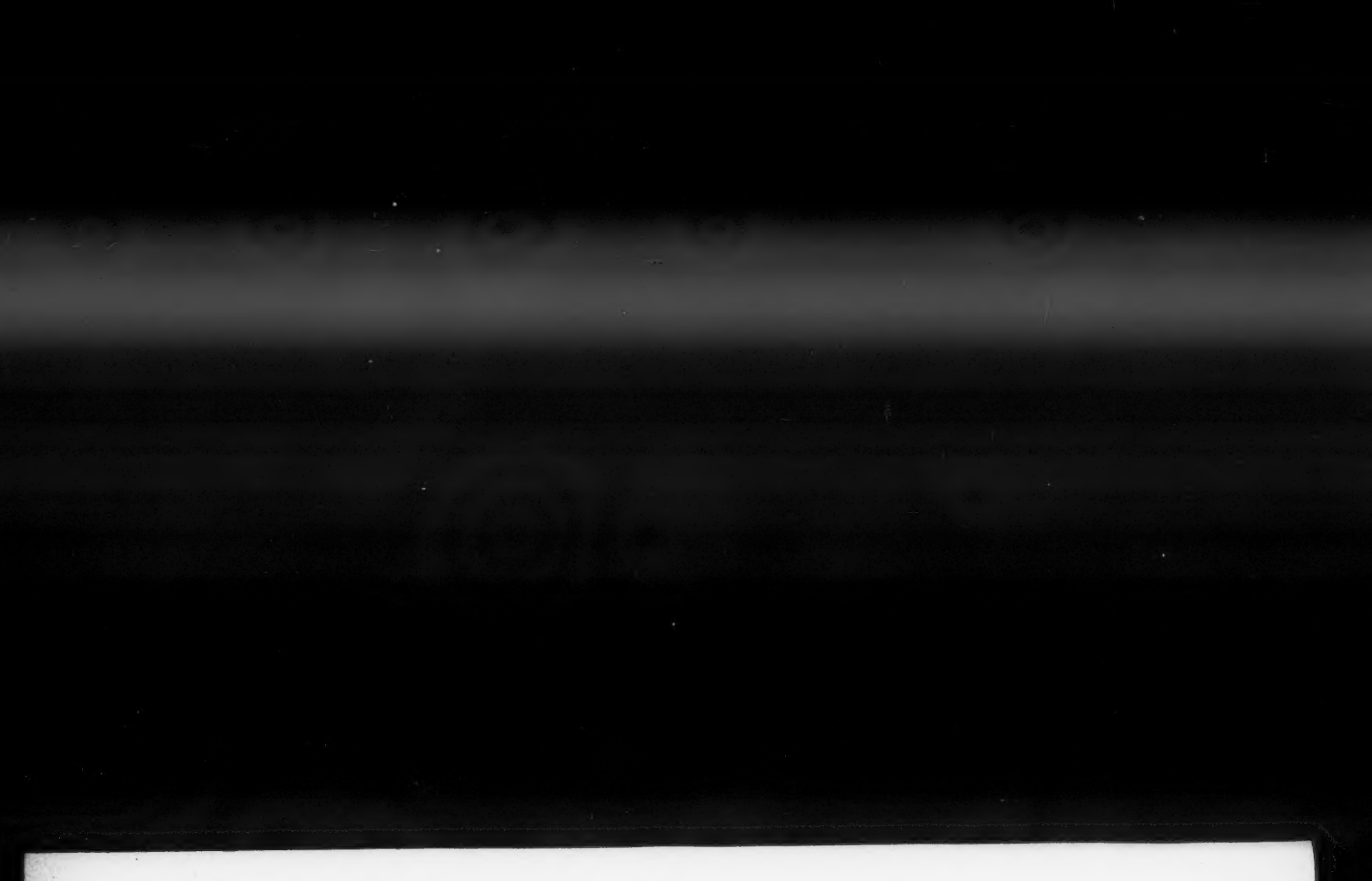
Modern Trends in Psychosomatic Medicine. Edited by DESMOND O'NEILL. 384 pages; 25 × 17 cm. 1955. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $10.50.

Neuropharmacology: Transactions of the First Conference, May 26, 27 and 28, 1954, Princeton, N. J. Edited by HAROLD A. ABRAMSON, M.D., Assistant Clinical Professor of Physiology, Columbia University College of Physicians and Surgeons, etc. 210 pages; 24 × 16 cm. 1955. Sponsored by the Josiah Macy, Jr. Foundation, New York, N. Y. Price, $4.25.

Principles of Medical Statistics. 6th Ed. By A. BRADFORD HILL, C.B.E., D.Sc., Ph.D., F.R.S., Professor of Medical Statistics in the University of London (London School of Hygiene and Tropical Medicine), etc. 314 pages; 22.5 × 14.5 cm. 1955. Oxford University Press, New York. Price, $4.00.

Prolonged and Perplexing Fevers. By CHESTER S. KEEFER, M.D., Physician-in-Chief and Director, Evans Memorial, Massachusetts Memorial Hospitals, etc.; and SAMUEL E. LEARD, M.D., Assistant Visiting Physician and Assistant Member, Evans Memorial, Massachusetts Memorial Hospitals, etc. 248 pages; 21 × 14 cm. 1955. Little, Brown & Company, Boston. Price, $5.50.

Reserpine in the Treatment of Neuropsychiatric, Neurological, and Related Clinical Problems (from the *Annals of the New York Academy of Sciences,* Volume 61, Art. 1, pages 1–280, April 15, 1955). Editor: ROY WALDO MINER; Conference Co-Chairmen: FREDRICK F. YONKMAN, FRANK L. MOHR, and JOCK L. GRAEME; Consulting Editor: FREDRICK F. YONKMAN. 280 pages; 23 × 15.5 cm. (paperbound). 1955. The New York Academy of Sciences, New York. Price, $3.50.

Should the Patient Know the Truth? A Response of Physicians, Nurses, Clergymen, and Lawyers. Edited by SAMUEL STANDARD, M.D., and HELMUTH NATHAN, M.D. 160 pages; 22.5 × 14.5 cm. 1955. Springer Publishing Company, Inc., New York. Price, $3.00 (hard cover); $2.00 (soft cover).

Untersuchung und Beurteilung des Herzkranken. By PROF. DR. H. W. KNIPPING, DOZ. DR. W. BOLT, DR. H. VALENTIN and DR. H. VENRATH. 461 pages; 24.5 × 16 cm. 1955. Ferdinand Enke Verlag, Stuttgart. Price, Geheftet DM 79.–; ganzleinen DM 83.–